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[2.2]PHANEPHOS-Ruthenium(II) Complexes: Highly Active Asymmetric Catalysts for the Hydrogenation of β-Ketoesters

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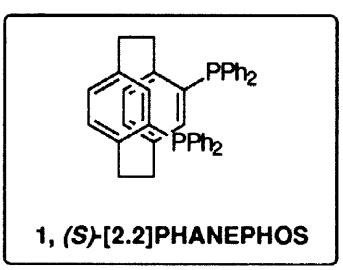
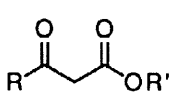
Abstract: The application of the planar chiral [2.2]PHANEPHOS ligand in the Ru(II)-catalyzed asymmetric hydrogenation of β-ketoesters gave up to 96% ee involving a practical and reproducible procedure using the defined and readily prepared [2.2]PHANEPHOS-Ru(II)bis(trifluoroacetate) salt in the presence of a halide source.

Almost 30 years have past since Knowles and Kagan first utilized chiral bisphosphines in asymmetric Rh-catalyzed hydrogenations.[1] Chiral bisphosphines have since proved to be among the most useful and versatile ligands in the area of organotransition metal-catalyzed reactions and the design of such bisphosphines remains as active an area of research as ever.[2] We have recently introduced [2.2]PHANEPHOS **1**:[3] a new C_2 symmetric bisphosphine ligand with a rigid [2.2]paracyclophane backbone. Application of [2.2]PHANEPHOS in both Rh-catalyzed asymmetric hydrogenations[4] and Pd-catalyzed aminations[5] have resulted in species of exceptional activity. It was therefore of great interest to apply our ligand to the Ru(II)-catalyzed hydrogenation of β-ketoesters (Scheme 1).



1, *(S)*-[2.2]PHANEPHOS

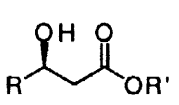


2

(S)-[2.2]PHANEPHOS-Ru(II)

MeOH / H_2O

H_2 / 50 psi



3

Scheme 1

The first highly successful reduction of these β-ketoesters used a BINAP-Ru(II) complex,[6] but it appeared that forcing conditions were required (100 atm/20°C or 4 atm/100°C) at the low catalyst loadings that were used. The use of added acid cocatalysts enabled the hydrogenations to be conducted at lower temperatures and pressures.[7] A number of later reports accounted the use of highly active bisphosphine-Ru(II) catalysts although, aside from the highly active and selective iPr-BPE-Ru(II) complex,[8] high catalyst loadings and increased temperatures (50 to 80°C) were used to achieve adequate reaction rates.[9]

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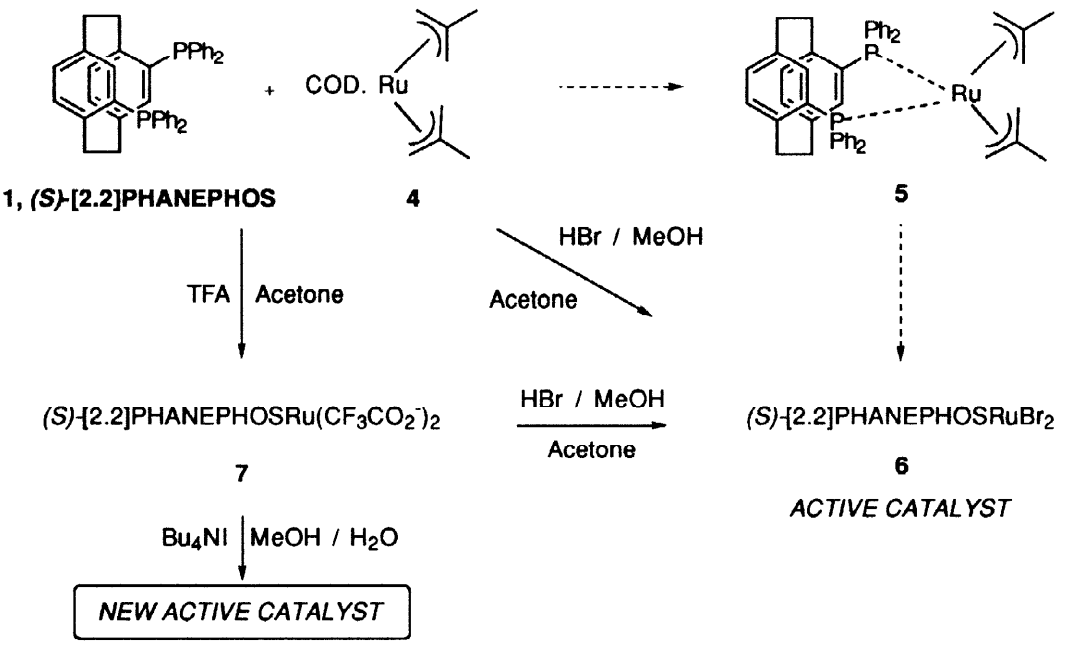
The bisphosphine-Ru(II) pre-catalysts have been prepared in a number of ways, but definite characterization of the active species in the catalytic cycle is missing.[10] Analysis of an empirically active catalyst by ^{31}P NMR indicates the presence of a large number of bisphosphine-Ru(II) complexes, making it difficult to identify the active species. Importantly, it appears that the active catalysts result from the coordinatively highly unsaturated complexes of the formula (bisphosphine)Ru(II)(halide)$_2$.

Bis(2-methylallyl)bisphosphineRu(II) complexes have been synthesized by the COD displacement of commercial bis(2-methylallyl)(COD)Ru(II) with the corresponding bisphosphine.[11] These complexes are subsequently treated with hydrogen bromide to afford active catalysts. Although in our hands the synthesis of the bis(2-methylallyl)BINAP-Ru(II) complex proceeded as reported, we were unable to isolate the analogous bis(2-methylallyl)[2.2]PHANEPHOS-Ru(II) complex **5** (Scheme 2). Following the *in situ* procedure for the *(S)*-[2.2]PHANEPHOS ligand, a complex mixture of species **6** was generated that was successful in catalyzing the hydrogenation of β-ketoesters with good to high enantioselectivity (70-94% ee). Unfortunately, the catalyst system generated by this procedure did not give consistent results and lost activity over several hours leading to a substantially less selective reducing system.[12]



Scheme 2

In order to isolate and characterize a [2.2]PHANEPHOS-Ru(II) complex, a solution of *(S)*-[2.2]PHANEPHOS and bis(2-methylallyl)(COD)Ru(II) in acetone was treated with trifluoroacetic acid.[13] A single compound **7**[14] was isolated that showed moderate selectivity and activity in the asymmetric hydrogenation of ethyl isobutyrylacetate (75% ee).[15] As expected, treatment of **7** with two equivalents of HBr gave a catalyst system that was equivalent to the *in situ* procedure reported above and this also lost activity over time.

In an alternative attempt to approach the necessary [2.2]PHANEPHOS-Ru(II)(halide)$_2$ stoichiometry, the reaction was conducted with *(S)*-[2.2]PHANEPHOS-Ru(II)bis(trifluoroacetate) **7** in the presence of Bu_4NI as a halide source. *Both the selectivity and activity of this system was superior to all others attempted and high conversions to >95%ee were achieved under neutral reaction conditions at temperatures as low as -10°C at 50psi H_2.*

A series of reactions was performed to probe the effect of the reaction parameters and the selectivity was found to be independent on the concentration of Bu_4NI (1 to 100 equivalents with respect to ruthenium) or substrate concentration (0.1 to 2 *M*). Only a slight pressure (20 to 1600 psi) and temperature (-10°C to 50°C) dependence was noted (selectivity increasing with decreasing temperature and pressure).[16]

A standard set of conditions was determined using ethyl isobutyrylacetate as a model substrate (50psi/ -5°C/ 0.4 to 0.8mol% cat./ 5 mol%BuN_4I/ 18h)[17] and a number of other commercially available substrates were screened. The system gave a consistently high enantioselectivity for a number of different alkyl substituted β-ketoesters under mild conditions (Table 1). Use of the *(S)*-[2.2]PHANEPHOS[18] ligand afforded a β-hydroxyester product of absolute configuration equivalent to that produced by *(R)*-BINAP, corresponding well with the Rh-catalyzed hydrogenation results. This would be expected as the relative positioning of the phosphorus atoms in these ligands is the same.[19]

Table 1: *(S)*-[2.2]PHANEPHOS-Ru(II)bis(trifluoroacetate) / tetrabutylammonium iodide catalyzed hydrogenation of β-ketoesters **2**.

entry	R	R'	ee(%) of **2**[a]	config[b]
a	Me	Me	96	*R*
b	Me	tBu	95	*R*
c	Me	Et	96	*R*
d	Et	Me	96	*R*
e	iPr	Et	95	*S*

All reactions went to completion in 18 hours at -5°C and 50 psi H_2. *(S)*-[2.2]PHANEPHOS-Ru(II)bis(trifluoroacetate) catalyst loading was 0.4 to 0.8 mol%, concentration of **2** was 1.5 to 2 *M*. The solutions contained 5 mol% tetrabutylammonium iodide . [a] Determination of ee with a Hewlett Packard 5890 GC using a FS-Lipodex-A 25 m × 0.25 mm column. [b] Absolute configuration determined by a comparison with the sign of optical rotation of literature compounds.

It is of interest to note the absence of any strong acids used in the immediate catalyst preparation. It seems that highly active and selective Ru(II)-species are generated simply by the presence of the iodide counterion. From a practical standpoint, the *(S)*-[2.2]PHANEPHOS-Ru(II)bis(trifluoroacetate) **7** could be stored up to several weeks in an argon atmosphere without noticable deterioration. The ease of generation of this catalytic system and the neutral reaction conditions make this a very attractive alternative to other reported methods.

In summary we have achieved high enantioselectivities for the Ru-catalyzed asymmetric hydrogenation of β-ketoesters utilizing the [2.2]PHANEPHOS ligand. A new catalyst system has been developed using [2.2]PHANEPHOS-Ru(II)bis(trifluoroacetate) **7** in the presence of tetrabutylammonium iodide. The high activity of this system allowed the reductions to be performed under neutral conditions at low pressures and at temperatures as low as -10°C.

References and Notes

1. (a) Knowles, W.S.; Sabacky, M.J. *J. Chem. Soc. Chem. Commun.* **1968**, 1445. (b) Dang, T.P.; Kagan, H.B. *J. Chem. Soc. Chem. Commun.* **1971**, 481. (c) Vineyard, B.D.; Knowles, W.S.; Sabacky, M.J.; Sasaki, M. *J. Am. Chem. Soc.* **1977**, *99*, 5946 (d) Horner, L.; Buthe, H. *Angew. Chem. Int. Ed. Engl.*. **1968**, *7*, 942.
2. (a) Sawamura, M.; Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9602. (b) Burk, M.J.; Feaster, J.E.; Nugent, W.A.; Harlow, *J. Am. Chem. Soc.* **1993**, *115*, 10125. (c) Togni, A. *Angew. Chem. Int. Ed. Engl.*. **1996**, *35*, 1475 and references cited therein. (d) Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1996**, *37*, 7995. (e) RajanBabu, T.V.; Casalnuovo, A.L. *J. Am. Chem. Soc.* **1996**, *118*, 6325. (f) Zhu, G.; Cao, P.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 1799.
3. [2.2]PHANEPHOS = 4,12-bis(diphenylphosphino)-[2.2]paracyclophane.
4. Pye, P.J.; Rossen, K.; Reamer, R.A.; Tsou, N.N.; Volante, R.P.; Reider, P.J. *J. Am. Chem. Soc.* **1997**, *119*, 6207
5. Rossen, K.; Pye, P.J.; Maliakal, A.; Volante, R.P. *J. Org. Chem.*. **1997**, *62*, 6462.
6. (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856. (b) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R.; *J. Am. Chem. Soc.* **1988**, *110*, 629. (c) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163. (d) Review: Ager, D.J.; Laneman, S.A. *Tetrahedron: Asymmetry* **1997**, *8*, 3327.
7. (a) Taber, D.F.; Silverberg, L.J. *Tetrahedron Lett.* **1991**, *32*, 4227. (b) King, S.A.; Thompson, A.S.; King, A.O.; Verhoeven, T.R. *J. Org. Chem.* **1992**, *57*, 6689.
8. iPr-BPE = 1,2-bis(*trans*-2,5-diisopropylphospholano)ethane. Burk, M.J.;Harper, G. P., Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423.
9. Genet, J.P.; Ratovelomanana-Vidal, M.C.; Cano de Andrade, X.; Pfister, P; Lenoir, J.Y. *Tetrahedron Lett.* **1995**, *36*, 4801.
10. For recent structural information see Wiles, J.A.; Bergens, S.H.; Young, V.G. *J. Am. Chem. Soc.* **1997**, *119*, 2940 and references cited therein.
11. Genet, J.P.; Mallart, S.; Pinel, C.; Juge, S.; Laffitte, J.A.; *Tetrahedron: Asymmetry* **1991**, *2*, 43.
12. Storing the solid generated overnight in an argon atmosphere (<0.1 ppm H_2O; <1 ppm O_2) led to a much less active species.
13. Heiser, B.; Broger, E.A.; Crameri, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 51.
14. [2.2]PHANEPHOS-Ru(II)bis(trifluoroacetate) **7**: ^{31}PNMR (161.87 MHz, CD_3OH) δ 46.7 (external 85% H_3PO_4 δ=0.0); ^{1}H NMR (399.87 MHz, CD_3OH) δ 7.91 (br t, J~8, 4 H), 7.55 (overlapping m, 4 H), 7.35 (t, J=7.6, 4 H), 7.26 (br t, J~7, 4 H), 7.25 (m, 2 H), 7.13 (t, J=7.6, 4 H), 6.53(br d, J=8.0, 2 H), 6.44 (m, 2 H), 2.66 (m, 4 H), 2.36 (ddd, J=13.7, 10.4, 3.4, 2 H), 1.80 (ddd, J=13.7, 10.4, 5.6, 2 H).
15. Use of the trifluoroacetate counter ion has previously been reported to give lower selectivities in the hydrogenation than the corresponding dihalide species, see Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons, Inc., New York, 1994.
16. Variations of up to 5% ee were observed.
17. ***General Procedure:*** A schlenk tube was charged with the substrate, Bu_4NI and $MeOH/H_2O$ (10:1) and the resulting solution degassed by three successive freeze-evacuate-thaw cycles. The tube was placed in an argon atmosphere glovebox (O_2 <1ppm) and the substrate solution transferred to a Fisher-Porter bottle containing the required amount of *(S)*-[2.2]PHANEPHOS-Ru(II)bis(trifluoroacetate). The bottle was sealed, brought out of the glovebox and cooled to -5°C. After three vacuum-hydrogen purge cycles the vessel was pressured to 50 psi H_2 and stirred vigorously (vaned stirrer bar) for 18 hours. Conversion was determined to be 100% by ^{1}H NMR. Enantioselectivity was determined by gc analysis.
18. For a definition of the chiral descriptor see: (a) Cahn, R.S.; Ingold, I.; Prelog, V. *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 385. (b) Pye, P.J.; Rossen, K. *Tetrahedron: Asymmetry* **1998**, *9*, 539.
19. Sakuraba, S.; Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1991**, *2*, 597.