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Highly Enantioselective Hydrogenation of Aromatic-Heteroaromatic Ketones

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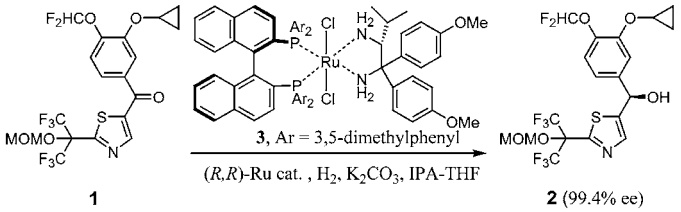
ABSTRACT



Asymmetric hydrogenation of ketone 1 using *trans*-$RuCl_2$[(*R*)-xylbinap][(*R*)-daipen] (3) as a catalyst afforded secondary alcohol 2 quantitatively and in 99.4% ee. Further exploration of the effect of the thiazole ring substitution revealed that the catalyst was highly effective for the enantioselective hydrogenation of 5-benzoyl thiazoles, which afforded corresponding alcohols in 92−99% ee. The same protocol was applicable to a variety of aromatic-heteroaromatic ketones to generate secondary alcohols in excellent enantioselectivities.

Enantiomerically pure alcohols, especially those bearing heterocycles, are important intermediates in the pharmaceutical industry and are usually available from the reduction of ketones either by chemical means or biotransformation.[1] Among the many protocols available for the transformation of prochiral ketones to chiral alcohols, the catalytic, asymmetric hydrogenation of ketones is one of the most efficient and cost-effective methods.[2] Chiral $RuCl_2$(diphosphine)(diamine) complexes pioneered by Noyori and co-workers, catalyze rapid, highly efficient asymmetric hydrogenation of a wide array of ketones in 2-propanol containing an alkaline base to afford the corresponding alcohols.[3] Recently, Burk et al. has reported that the ruthenium complexes based upon the novel PhanePhos ligands also serve as efficient catalyst precursors for highly enantioselective hydrogenation of ketones.[4] Other ligands have also emerged that are useful for the asymmetric hydrogenation of prochiral ketones.[5] Although several methods for the asymmetric hydrogenation of ketones exist, the enantioselective hydrogenation of aromatic-heteroaromatic or bis heteroaromatic ketones re-

(1) (a) Roy, S.; Alexandre, V,; Neuwels, M,; Le Texier, L. *Adv. Synth. Catal.* **2001**, *343*, 738. (b) Roszkowski, A. P.; Govier, W. M. *Pharmacologist* **1959**, *1*, 60. (c) Barouth, V.; Dall, H,; Petal, D.; Hite, G. *J. Med. Chem.* **1971**, *14*, 834. (d) Huang, W.; Pu, L. *Tetrahedron Lett.* **2000**, *41* (2), 145. (e) Salvi, N. A.; Chattopadhyay, S. *Tetrahedron* **2001**, *57* (14), 2833. (f) Masui, M.; Shioiri, T. *Synlett.* **1997**, *3*, 273. (g) Miyashita, A.; Matsuoka, Y.; Suzuki, Y.; Iwamato, K.; Higashino, T. *Chem. Pharm. Bull.* **1997**, *45*, 1235. (h) Okano, K.; Murata, K.; Ikariya, T. *Tetrahedron Lett.* **2000**, *41*, 9277. (i) Takeshita, M.; Yoshida, S.; Sato, T.; Akutsu, N. *Heterocycles* **1993**, *35*, 879. (j) Vasse, J. L.; Charpentier, P.; Levacher, V.; Dupas, G.; Queguiner, G.; Bourguignon, J. *Synlett.* **1998**, *10*, 1144. (k) Takemoto, M.; Achiwa, K. *Chem. Pharm. Bull.* **1994**, *42*, 802. (l) Bolm, C.; Muniz, K. *Chem. Comm.* **1999**, *14*, 1295. (m) Okano, K.; Murata, K.; Ikariya, T. *Tetrahedron Lett.* **2000**, *41*, 9277.

(2) (a) Noyori, R. *Adv. Synth. Catal.* **2003**, *345*, 15. (b) Wills, M.; Hannedouche, J. *Curr. Opin. Drug Dis. Dev.* **2002**, *5* (6), 881. (c) Chaplin, D.; Harrison, P.; Henschke, J. P.; Lennon, I. C.; Meek, G.; Moran, P.; Pilkington, C. J.; Ramsden, J. A.; Watkins, S.; Zanotti-Gerosa, A.. *Org. Process Res. Dev.* **2003**, *7* (1), 89. (d) Everaere, K.; Mortreux, A.; Carpentier, J. *Adv. Synth. Catal.* **2003**, *345*, 67. (e) Blaser, H.; Malan, C.; Pugin, B.; Spindler, F; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. (f) Noyori, R.; Okhuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40.

(3) (a) Doucet, H; Ohkuma, T.; Murata, K.; Yokozawa, M.; Katayama, E.; England, a. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703. (b) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675. (c) Ohkuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659. (d) Ohkuma, T.; Koizumi, M.; Yoshida, M.; H.; Noyori, R. *Org. Lett.* **2000**, *2*, 1749.

(4) Burk, M. J.; Hems, W.; Herzberg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.* **2000**, *2* (26), 4173.

(5) (a) Xie, J.-H.; Wang, L,-X.; Fu, Y.; zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2003**, *125*, 4404. (b) Wu, J.; Chen, H.; Kwok, W.; Guo, R.; Zhou, Z.; Yeung, C.; Chan, A. S. C. *J. Org. Chem.* **2002**, *67*, 7908.

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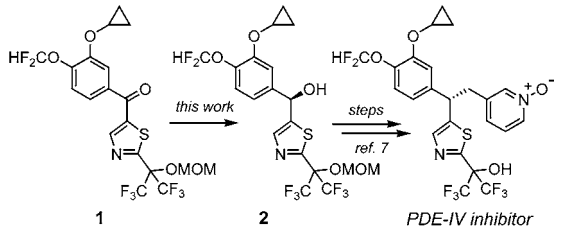
mains fairly unprecedented. Herein, we wish to disclose a general method for the highly efficient, enantioselective hydrogenation of these ketones.[6]

In the course of our recent drug development program for a potent PDE-IV inhibitor (Scheme 1), we sought to convert

Scheme 1



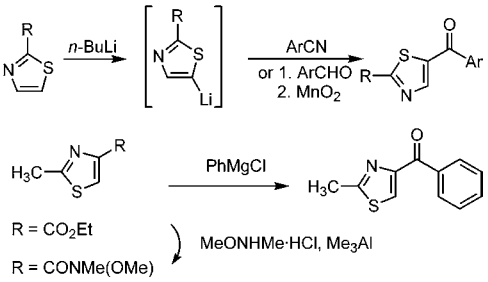
ketone **1** to alcohol **2** in a catalytic, enantioselective manner.[7] The enantioselective reduction of ketone **1** was initially carried out using super stoichiometric amounts of BINAL-H to give the alcohol in 89−96% ee.[8] Though the reaction performed well on scale-up, it also introduced 3 equiv of BINOL that need to be recycled, and a more efficient, catalytic method was desired. To this end, we attempted the reduction of ketone **1** under a standard set of reaction conditions (40 psi H_2, K_2CO_3/Ru = 25/1, S/C = 50/1, 20 mL/g solution of ketone in i-PrOH) using *trans*-$RuCl_2$[(*R*)-xylbinap][(*R*)-daipen] (**3**) as a catalyst.[2f,3] The reduction of ketone **1** performed exceptionally well on our very first attempt, which gave **2** in 99.4% ee in quantitative yield.[9,10]

Our initial efforts were to optimize this reduction in terms of catalyst loading since S/C at 50/1 was not practical for scale-up. After considerable optimization, we found that the reaction was best carried out under the following conditions: 40 psi H_2, K_2CO_3/Ru = 25/1, S/C = 1000/1, 4 mL/g solution of ketone in 4:1 *i*-PrOH−THF at ambient temperature to give alcohol **2** in >99% ee.[11] We felt that at S/C 1000/1, the process became viable for the preparation of this advanced pharmaceutical intermediate. The perfect match between ketone **1** and catalyst **3** prompted us to seek the structural origin of the enantioselectivity.

We were amazed by the exceedingly high enantioselectivity for the hydrogenation of ketone **1** since it is not obvious to predict on the basis of the structural motif of this fully substituted aromatic-heteroaromatic ketone. Ru-catalyzed enantioselective hydrogenation of benzophenones was reported to provide benzhydrols in high enantioselectivity provided that one aromatic ring was ortho-substituted.[3a] The fact that ketone **1** does not possess any substituents at the ortho position made us wonder if the asymmetric induction originated from the substitution pattern on the thiazole ring.

We speculated that the high asymmetric induction may largely be controlled by the steric effect of the bistrifluoromethyl MOM ether group at the 2-position of the thiazole ring.[12] To study the steric effect of the 2-substituent on the enantioselectivity of hydrogenation, a variety of thiazole ketones were prepared either by direct condensation of 5-lithium thiazole species with aromatic nitriles or with aldehydes followed by oxidations using MnO_2.[13] 4-Benzothiazole was prepared from the addition of phenylmagnesium chloride to the thiazole Weinreb amide. The results of their asymmetric hydrogenations using catalyst **3** are summarized in Table 1.

Scheme 2. Formation of 5-Thiazole Ketone from Either ArCN or ArCHO



Hydrogenation of MOM-protected benzoyl thiazole **4a** afforded the corresponding alcohol **5a** in 97.5% ee and 96% yield. This result suggests that both alkoxyl groups in the phenyl ring have no effect on the enantioselectivity in the reduction of ketone **1**. The hydrogenation was equally efficient for the TBS-substituted ketone, which afforded aldohol **5b** (R = TBS) in 97.5% ee. Hydrogenation of ketone **6**, containing bulky 2-dioxalanyl substituent, afforded alcohol **7** in 92% ee and 97% yield. The ee of this alcohol could be easily upgraded to >99% by crystallization from EtOAc−hexanes. Similarly, hydrogenation of ketone **8a** afforded alcohol **9a** in excellent yield and enantioselectivity (99% ee).

(6) (a) Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M; Müller, R.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *1*, 131. (b) Broger, E.; Hofheinz, W.; Meili, A. (Hoffmann-La Roche) Eur. Pat. 553778, 1993.

(7) Friesen, R. W.; Ducharme, Y.; Ball, R. G.; Blouin, M.; Boulet, L.; Cote, B.; Frenette, R.; Girard, M.; Guay, D.; Huang, Z.; Jones, T. R.; Laliberte, F.; Lynch, J. J.; Mancini, J.; Martins, E.; Masson, P.; Muise, E.; Pon, D. J.; Siegl, P. K. S.; Styhler, A.; Tsou, N. N.; Turner, M. J.; Young, R. N.; Girard, Y. *J. Med. Chem.* **2003**, *46*, 2413.

(8) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6 (22), 6709.

(9) Absolute configuration of alcohol **2** was assigned as (*R*)- on the basis of NMR spectra of its methoxyphenyl acetic acid derivatives and its conversion to compound **3** via inversion chemistry (to be published).

(10) Seto, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915.

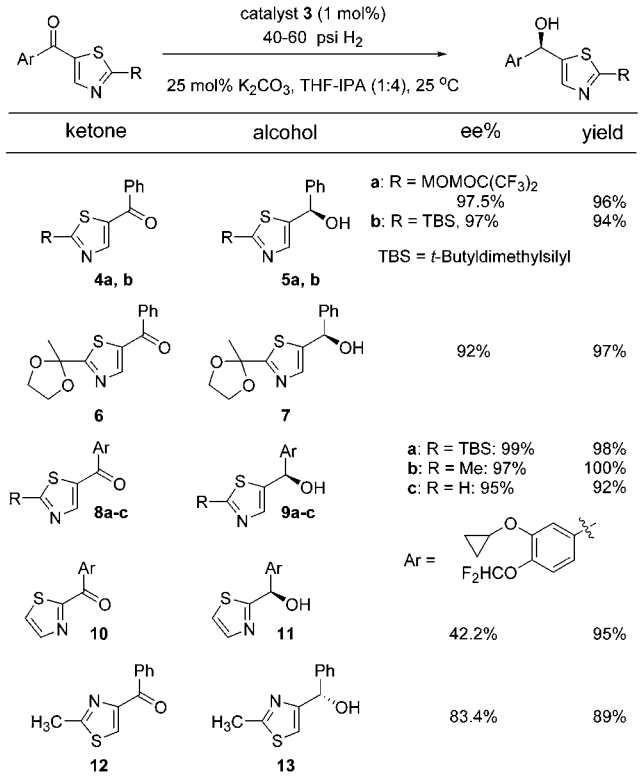
(11) THF was used as a cosolvent to improve the solubility of ketone **1** in IPA. The reaction became sluggish when lowering the catalyst loading to S/C 10 000/1. A typical hydrogenation follows. To ketone **1** (1 mmol) in 2−3 mL of THF−IPA (1:4) was added powdered K_2CO_3 (0.25 mmol). The mixture was degassed three times via vacuum/nitrogen purge, followed by addition of catalyst **3** (0.01 mmol). The mixture was hydrogenated at 40−60 psi at ambient temperature for 24−48 h. Removal of solvents followed by SiO_2 chromatography afforded alcohol **2**.

(12) Bioreduction of a bulky ketone, 1-phenyl-1-(2-phenylthiazol-5-yl)-methanone, was reported to give alcohol in up to 96% ee, partially attributed to the size discrimination between the phenyl group and 2-phenyl thiazole group (ref 1a).

(13) (a) Frey, L. F; Marcantonio, K. M., Chen, C.-y, Wallace, D.; Murry, J. A.; Dolling, U. H.; Grabowski, E. J. J.; Tan, L.; Chen, W. *Tetrahedron* **2003**, 59, 6363. (b) Marcantonio, K. M.; Frey, L. F.; Chen, C.-y.; Murry, J. A. *Tetrahedron Lett.* **2002**, *43*, *8845*.

All these results supported our initial hypothesis of a strong steric effect of the 2-position on enantioselectivity. However, we were very surprised to find that hydrogenation of sterically less demanding ketones such as **8b** (R = Me) and **8c** (R = H) worked equally well to give alcohols in 97 and 95% ee, respectively. These results clearly ruled out the steric effect of the 2-substituents of thiazole ketones on the asymmetric induction that we had initially speculated. On the basis of the results summarized in Table 1, we conclude that reduction of 5-thiazole aromatic ketone using catalyst **3** would lead to high enantioselectivity.

Table 1. Effect of Substitution on Enantioselectivity



[a] All reactions were carried out using the procedure described in ref 11.

However, we discovered a significant dependence of the enantioselectivity on the thiazole substitution pattern. In contrast to ketone **8c**, hydrogenation of 2-benzothiazole **10** under the same reaction conditions afforded alcohol **11** in modest ee (42.2%). Reduction of 4-thiazole ketone **12**, however, gave alcohol **13** in 83.4% ee and 89% yield in (*S*)-configuration. Interestingly, the sense of asymmetric induction for 4-benzothiazole (**12**) is opposite to that of the 5-benzothiazole counterparts.

The remarkable enantioselectivity of the hydrogenation of prochiral ketone **1** prompted us to extend the application of the catalyst **3** to other aromatic-heteroaromatic ketones. We next sought to apply this method to arylpyridyl ketones since practical stereoselective syntheses of optically active pyridyl aromatic alcohols are rarely reported.[1d−m,14] To our knowledge, the enantioselective hydrogenation of these ketones has mainly been reported for the alkylpyridyl ketones.[3d,4,5] The asymmetric transfer hydrogenation using a chiral Ru(II) complex of benzoyl 2-pyridine was also reported; however, the process gives the alcohol in very poor selectivity (9% ee).[1m]

Surprisingly, hydrogenation of ketones **14** and **16** using conditions[11] reported in Table 1 gave decent enantioselectivity despite the isosteric nature of the Ar group and pyridinyl ring. For example, enantioselective hydrogenation of 4-benzopyridine (**14a**) and 3-benzopyridine (**14b**) afforded the corresponding (*R*)-alcohols, **15a** and **15b**, in 57.2 and 73.3% ee, respectively. Interestingly, the sense for the asymmetric induction of 2-benzopyridine (**16a**) was opposite to that of **14a**,**b**, as the (*S*)-alcohol (**17a**) was obtained in 74.8% ee. The enantioselectivity for the hydrogenation of derivatives of **16** was greatly influenced by the para substitution on the phenyl ring. Hydrogenation of **16b** (X = Cl) afforded alcohol **17b**[1b,c,15] in lower ee (60.6 vs 74.8% for **16a**), whereas the hydrogenation of **16c** (X = OMe) afforded **17c**[16] in higher ee (89.5 vs 74.8% for **16a**). The sense of asymmetric induction of **16a**−**c** is opposite to that of **14a**,**b**, suggesting that the asymmetric induction may be controlled by the coordination of the 2-pyridine nitrogen to the catalyst. The substitution effect on the enantioselectivity for 2-benzopyridines is quite significant and merits further investigation.

Since the documented high enantioselectivity for the hydrogenation of unsymmetrical diaryl ketones relies on the presence of an ortho substituent in one of the aromatic rings,[3c] we reasoned that the same steric effect may be applied to the pyridinyl ketones to override the electronic effect. Indeed, introduction of the methyl group ortho to the carbonyl moiety improved the enantioselectivity dramatically, as reduction of ketone **18** gave alcohol **19** in 98.7% ee.[17] The sense of asymmetric induction in the reduction for ketone **18** is the same as that observed for the reduction of 2-methylbenzophenone using catalyst **3**.[18] This indicates that the steric effect dominates for the reduction. A similar result was obtained for quinoline ketone, which gave alcohol in 91.4% ee. The methyl group in **18** and the fused phenyl ring in ketone **20** apparently generate sufficient stereobias between the aromatic groups to effect good enantiodifferentiation for the reduction.

We also demonstrated that this procedure can be extended to several classes of bis-aromatic ketones. For example, hydrogenation of pyridinyl-thiazole ketone **22** afforded (*R*)-

(14) Bioreduction of 2-,3-,4-pyridnyl phenyl ketones were reported to give corresponding alcohols in a wide range of enantioselectivities (3 to 100% ee). Reduction of 4-pyridyl phenyl ketone using chiral amino alcohols and trimethyl borate was reported to give the alcohol in 61−83% ee.

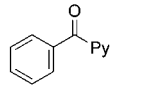
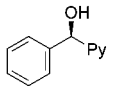
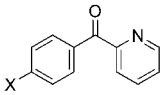
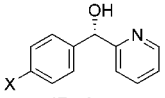
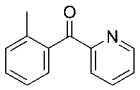
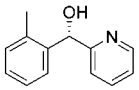
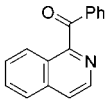
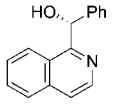
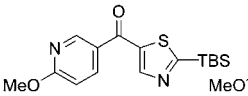
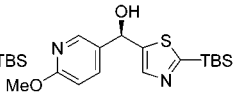
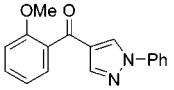
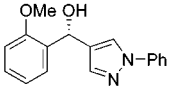
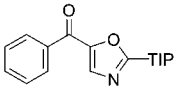
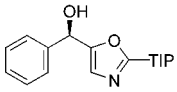
(15) Alcohol **17b** is a precursor to a medicinally useful histamine H1 antagonist (*S*)-carbinoxamine. Direct reduction of 2-benzopyridine using oxazborolidine led to racemic alcohol and thus required for the protection of nitrogen by forming *N*-alkylpyridinium salt to achieve high selectivity, see: Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996**, *37*, 5675.

(16) Absolute configuration of **17c** was assigned as (*S*)- on the basis of its optical rotation; see: Bojadziev, S. E.; Tsankov, D. T.; Ivanov, P. M.; Berova, N. D. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2651.

(17) Absolute configuration of **19** was unambiguously established on the basis of X-ray analysis on its (*R*)-methoxy phenyl acetate.

(18) Absolute configuration of **19** was unambiguously established on the basis of X-ray analysis on its (*R*)-methoxy phenyl acetate.

Table 2. Hydrogenation of Bis-aromatic Ketones[a,b]

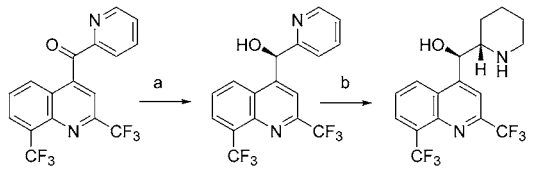
ketone	alcohol	ee%	yield
 **14a, b**	 **15a, b**	**a**: 4-Py, 57.2% **b**: 3-Py, 73.3%	100% 94%
 **16a, b, c**	 **17a, b, c**	**a**: X = H, 74.8% **b**: X = Cl, 60.6% **c**: X = OMe, 89.5%	87% 98% 100%
 **18**	 **19**	98.7%	93%
 **20**	 **21**	91.4 %	87%
 **22**	 **23**	94.4%	100%
 **24**	 **25**	93.6%	65%[c]
 **26**	 **27**	**>99.5%**	94% TIP = trisiopropylsilyl

[a] Same conditions as described in ref 11. [b] Absolute configurations of **15** and **17** were assigned on the basis of optical rotations. [c] Ketone **24** was recovered (30%).

alcohol **23** quantitatively in 94.4% ee. The asymmetric induction for the hydrogenation of **22** is the same as that for 5-benzoyl thiazole ketones, as confirmed by the X-ray analysis. Hydrogenation of imidazole-ketone **24**[19] gave alcohol **25** in 93.6% ee (67% yield). Finally, hydrogenation of TIP-substituted oxazole-phenyl ketone **26** afforded alcohol **27** in 94% yield in nearly perfect enantioselectivity (>99.5% ee).

With an efficient method for the asymmetric hydrogenation in hand, we sought to apply this procedure to the synthesis of chiral alcohol **29**, which serves as the penultimate intermediate to Roche's antimalarial drug, (*R*,*S*)-mefloquine.[20] Asymmetric hydrogenation of ketone **28** under conditions similar to those cited in Table 1 proceeded uneventfully to give (*R*)-**29** in 88% ee and 92% isolated yield. This unoptimized result is comparable to the best example (**29** in 92% ee and 86% conversion) obtained from the Rh(I)-catalyzed hydrogenation using a variety of C-2 diphosphine ligands.[6]

Scheme 3. Asymmetric Synthesis of (*R*,*S*)-Mefloquine[a]



[a] Conditions: (a) 1 mol% (*S*,*S*)-**3**, 25 mol% K_2CO_3, IPA−THF, 4:1, 25 °C, 25 psi of H_2; (b) Pt, H_2, HCl, ref 6.

In summary, we have identified a highly efficient and cost-effective protocol for the catalytic, enantioselective hydrogenation of ketone **1** to alcohol **2** using catalyst **3**. This catalyst proved to be exceptionally effective toward the enatioselective hydrogenation of 5-benzoyl thiazoles regardless of the size of 2-substituents. The reaction was extended to a variety of aromatic-heteroaromatic ketones, as well as to bis-heterocyclic ketones. Many structurally interesting heterocyclic benzylhydrols were readily prepared in a catalytic manner in high enantioselectivity. We believe that the broad scope of this catalyst toward the hydrogenation of bis-aromatic ketones will lead to more applications of the system to structurally diverse substrates.

Supporting Information Available: All the new compounds were fully characterized by ^1H and ^{13}C NMR spectra. Absolute configurations for compounds **7**, **9b**, **13**, **19** (as its MPA ester), and **23** were unambiguously assigned based on the X-ray analysis (ORTEP drawings attached). The enantiomeric excess for the alcohols was assayed by chiral HPLC methods. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0360795

(19) Ketone **24** was prepared quantitatively by methylation of the corresponding phenol using MeI in acetone in the presence of K_2CO_3.

(20) Ohnmacht, C. J.; Patel, A. R.; Lutz, R. E. *J. Med. Chem.* **1971**, *14*, 926.