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Palladium-Catalyzed Asymmetric Hydrogenation of Functionalized Ketones

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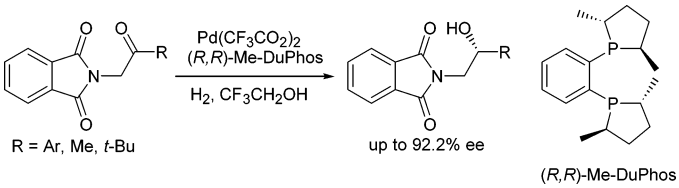
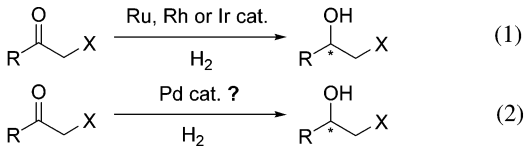
ABSTRACT



A novel catalytic system for asymmetric hydrogenation of functionalized ketones has been developed using a Pd/bisphosphine complex as the catalyst in 2,2,2-trifluoroethanol. The reaction exhibits high enantioselectivity, and up to 92.2% ee was obtained.

Transition-metal-catalyzed asymmetric synthesis is one of the most powerful methods for preparing a wide range of enantiomerically pure compounds and has turned into one of the most important fields at the interface between organic synthesis and organometallic chemistry.[1] Among the different catalytic methods, asymmetric hydrogenation utilizing molecular hydrogen to reduce prochiral substrates is one of the most efficient.[1,2] In the past 30 years, there were many successful examples and high enantioselectivities were achieved in asymmetric hydrogenation of prochiral ketones to yield optically active secondary alcohols by using chiral Ru, Rh, and Ir complexes (eq 1).[1−3]



(1)

(2)

Recently, Pd complexes have become indispensable tools for both common and state-of-the art organic synthesis.[4] Although a large number of Pd-based catalytic systems have been developed for many kinds of reactions of a wide range of compounds,[4,5] palladium chemistry has still not achieved its full potential. The search for the improvement of palladium-catalyzed reactions continues with the goal of increasing the diversity of possible substrates and reaction types. For example, very little attention has been paid to palladium-catalyzed homogeneous asymmetric hydrogenation reactions, although many successful examples of heterogeneous asymmetric hydrogenation reactions catalyzed by Pd(0) have been well documented in the literature.[6] Amii and co-workers reported a good enantioselective hydrogenation of α-fluorinated iminoesters in 2,2,2-trifluoroethanol using $Pd(CF_3CO_2)_2$/BINAP as catalyst with up to 91% ee.[7] In 2003,

(1) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999. (b) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

(2) (a) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008. (b) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40. (c) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998. (d) Rossen, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4611. (e) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(3) Ir-catalyzed asymmetric hydrogenation of ketones: Zhang, X.; Taketomi, T.; Yoshizumi, T.; Kumobayashi, H.; Akutagawa, S.; Mashima, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 3318.

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(5) Recent reviews about Pd chemistry: (a) Special issue: Palladium Chemistry in 2003: Recent Developments. *J. Organomet. Chem.* **2003**, *687*, 209−590. (b) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453.

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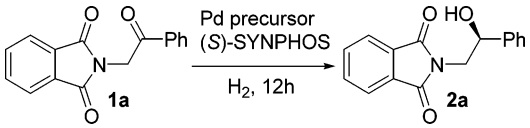
Alper et al. reported palladium-catalyzed asymmetric double carbohydroamination of iodobenzene for the synthesis of chiral α-aminoamides with high enantioselectivity. The catalytic cycle they suggested involved palladium-catalyzed asymmetric hydrogenation of α-iminoamide intermediates; however, no evidence was given.[8] More recently, Raja and Thomas reported a heterogeneous asymmetric hydrogenation of α-ketoesters with catalyst Pd(allyl)diamino triflate anchored to the inner wall of mesoporous supports by the surface-bound triflate counterion with 67% ee, but in homogeneous form, only 55% ee was obtained.[9] So, the search for an efficient homogeneous palladium catalytic system for asymmetric hydrogenation of ketones is still a challenge. In the course of our research on asymmetric hydrogenation of heteroaromatic compounds,[10] we became interested in exploring Pd-catalyzed asymmetric hydrogenation of ketones (eq 2). Herein, we report our preliminary results of asymmetric hydrogenation of a class of functionalized ketones using homogeneous palladium catalysts, where up to 92.2% ee was achieved.

The enantioslective hydrogenantion of protected amino ketones is one of the efficient methods to obtain the corresponding chiral amino alcohols, which are important compounds as biologically active molecules and chiral auxiliaries.[11] High enantioselectivity have been achieved upon asymmetric hydrogenation of α-phthalimide ketones[12] with Ru−phosphine complexes.[13] We chose 2-phthalimide-1-phenylethanone (**1a**) as a hydrogenation model substrate and carried out our initial experiments employing a Pd-$(OCOCF_3)_2$/(*S*)-SYNPHOS system in 2,2,2-trifluoroethanol (TFE) under 1000 psi of hydrogen. It was pleasing to find that a promising result (77.5% ee and conversion 91%) was obtained (entry 1, Table 1).

We further performed a systematic investigation on the asymmetric hydrogenation of **1a**. The results are summarized in Table 1. First, the effect of the temperature and the pressure was studied. When the reaction was carried out at 50 °C, slightly lower enantioselectivities were obtained (entry 2). Hydrogen pressure had no dramatic effect on enantioselectivity (entries 2−5). Second, the effect of solvent was also investigated; it was found that this reaction was strongly solvent-dependent (entries 4, 6−12). Only TFE is most effective in terms of the conversion and enantioselectivity, which agreed with Pd-catalyzed asymmetric hydrogenation of α-fluorinated iminoesters reported by Amii et al.[7a] 1,2-Dichloroethane (DCE) gave low conversion with similar enantioselectivities (entry 10), and other solvents led to low activity. Other Pd catalyst precursors were also tested in the reaction (entries 13−16). $Pd(CH_3CO_2)_2$ gave moderate conversion with slightly lower ee (entry 13), whereas cationic $Pd(OTf)_2$ provided a result equivalent to that of $Pd(CF_3CO_2)_2$ (entries 4 vs 14). Metal precursors with halide had also no catalytic activity (entry 15), which might be ascribed to the strong coordinated character of chloride ion, which occupied the coordination site of the central metal palladium, which might play an important role in the activity. Pd(0) species was also unable to catalyze this reaction (entry 16).

Subsequently, we turned our attention to the effect of various commercially available chiral ligands (Figure 1) on the asymmetric hydrogenation using $Pd(CF_3CO_2)_2$ as metal precursor in TFE under 200 psi of hydrogen at 50 °C (Table 2). The results showed that monophosphine ligand MOP (**L2**)

Table 1. Optimizaion of Reaction Conditions for Pd-Catalyzed Asymmetric Hydrogenation of α-Phthalimide Ketone[a]



entry	Pd precursor	solvent	H_2 (psi)	conv (%)[b]	ee (%)[c]
1[d]	$Pd(CF_3CO_2)_2$	TFE	1000	91	77.5
2	$Pd(CF_3CO_2)_2$	TFE	1000	>95	77.0
3	$Pd(CF_3CO_2)_2$	TFE	600	>95	76.0
4	$Pd(CF_3CO_2)_2$	TFE	200	>95	76.4
5	$Pd(CF_3CO_2)_2$	TFE	40	>95	75.2
6	$Pd(CF_3CO_2)_2$	*i*-PrOH	200	<5	N/A
7	$Pd(CF_3CO_2)_2$	EtOH	200	<5	N/A
8	$Pd(CF_3CO_2)_2$	MeOH	200	<5	N/A
9	$Pd(CF_3CO_2)_2$	THF	200	<5	N/A
10	$Pd(CF_3CO_2)_2$	DCE	200	16	74.4
11	$Pd(CF_3CO_2)_2$	acetone	200	<5	N/A
12	$Pd(CF_3CO_2)_2$	toluene	200	<5	N/A
13	$Pd(CH_3CO_2)_2$	TFE	200	44	74.2
14[e]	$Pd(OTf)_2$	TFE	200	>95	76.4
15[e]	$PdCl_2$	TFE	200	<5	N/A
16	$Pd_2(dba)_3$	TFE	200	<5	N/A

[a] Unless otherwise stated, reactions were performed on a 0.25-mmol scale: Pd precursor 2 mol %, (*S*)-SYNPHOS 2.4−3.0 mol %, 12 h, 50 °C (oil bath temperature). [b] Determined by ^{1}H NMR analysis of the crude product. [c] Determined by HPLC analysis. [d] The reaction was carried out at room temperature. [e] Pure complex (2 mol %)[14] was used.

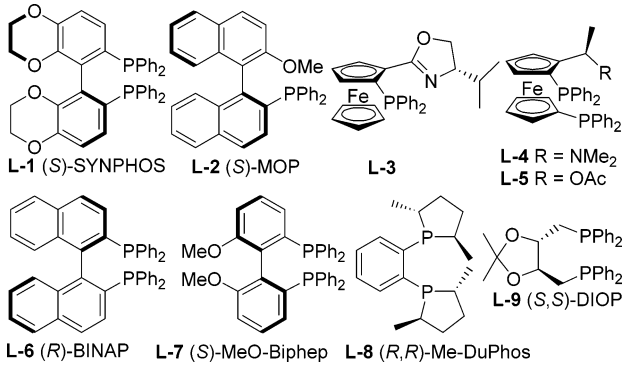
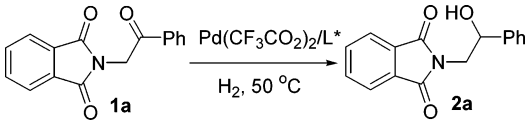


Figure 1. Various chiral ligands.

(6) Recent literature on heterogeneous Pd enantioselective hydrogenation. Reviews: (a) Studer, M.; Blaser, H.-U.; Exner, C. *Adv. Synth. Catal.* **2003**, *345*, 45. (b) Baiker, A. *J. Mol. Catal. A: Chem.* **2000**, *163*, 205. Communications: (c) Glorius, F.; Spielkamp, N.; Holle, S.; Goddard, R.; Lehmann, C. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2850. (d) Mhadgut, S. C.; Bucsi, I.; Toeroek, M.; Toeroek, B. *Chem. Commun.* **2004**, 984. (e) Raynor, S. A.; Thomas, J. M.; Raja, R.; Johnson, B. F. G.; Bell, R. G.; Mantle, M. D. *Chem. Commun.* **2000**, 1925.

Table 2. Ligand Screening for Pd-Catalyzed Asymmetric Hydrogenation of α-Phthalimide Ketone[a]



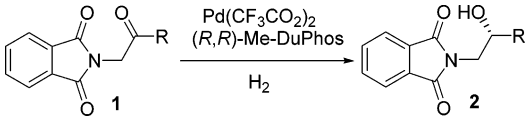
entry	ligand	conv (%)[b]	ee (%)[c]	configuration[d]
1	**L1**	>95	76.4	*S*
2[e]	**L2**	<5	N/A	
3	**L3**	<5	N/A	
4	**L4**	<5	N/A	
5	**L5**	22	48.6	*R*
6	**L6**	82	74.3	*R*
7	**L7**	>95	79.3	*S*
8	**L8**	>95	91.7	*R*
9	**L9**	17	58.4	*R*

[a] Unless otherwise stated, reactions were performed on a 0.25-mmol scale: $Pd(CF_3CO_2)_2$ 2 mol %, ligand 2.4 mol %, H_2 200 psi, TFE, 12 h, 50 °C (Oil bath temperature). [b] Determined by ^1H NMR analysis of the crude products. [c] Determined by HPLC analysis. [d] Determined by comparison of rotation sign with literature data. [e] **L2** (4.4 mol %) was used.

had almost no catalytic activity (entry 2). P,N-ligand **L3** and N-containing bisphosphine ligand **L4** also showed very low activity (entries 3 and 4). Those other chiral bisphosphine ligands tested exhibited moderate to high conversion (entries 1, 5−9), whereas the best result (up to 91.7% ee with more than 95% conversion) was achieved with electron-rich (*R,R*)-Me-DuPhos **L7** (entry 7).

Under optimized condition, a variety of substituted α-phthalimide ketones were hydrogenated to yield their corresponding secondary alcohols (Table 3).[15] Both electron-deficient and electron-rich aryl ketones can be hydrogenated in high enantioselectivities (entries 1−8); up to 92.2% ee of hydrogenated products were obtained for *para*-substituted **1b** (entry 2) and **1c** (entry 3). For *o*-methoxy-substituted aryl ketone (**1g**), slightly lower enantioselectivities were obtained (entry 7). Alkyl ketones and even simple methyl ketone gave good asymmetric induction (entries 9 and 10). For substrate

Table 3. Asymmetric Hydrogenation of α-Phthalimide Ketones Catalyzed by a $Pd(OCOCF_3)_2$/(*R,R*)-Me-DuPhos System[15]



entry	R of **1**	temp (°C)[a]	conv (%)	ee (%)
1	C_6H_5 (**1a**)	50	>95	91.7
2	*p*-FC_6H_4 (**1b**)	50	>95	92.2
3	*p*-MeC_6H_4 (**1c**)	50	>95	92.2
4	*p*-PhC_6H_4 (**1d**)	75	>95	90.4
5[b]	*p*-$MeOC_6H_4$ (**1e**)	50	94	75.2
6	*m*-$MeOC_6H_4$ (**1f**)	50	>95	92.0
7	*o*-$MeOC_6H_4$ (**1g**)	75	>95	80.4
8	2-naphthyl (**1h**)	75	72	88.2
9	Me (**1i**)	50	>95	89.8
10	*t*Bu (**1j**)	50	>95	88.0
11	*p*-BrC_6H_4 (**1k**)	50		N/A

[a] Oil bath temperature. [b] (*S*)-SYNPHOS was used.

(**1k**) with a bromo goup (entry 11), no desired product was obtained under the standard condition; the reason might be catalyst poisoning for oxidative addition of palladium and aromatic bromine. It is noteworthy that this is the first example with a Pd/bisphosphines complex as a homogeneous asymmetric hydrogenation catalyst of ketones.

To further expand the utility of this Pd-catalyzed asymmetric hydrogenation of ketones, other ketones have been examined under standard condition (Figure 2).[15] Hydrogena-

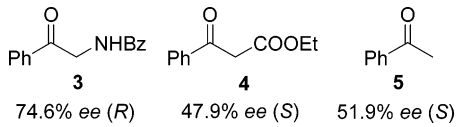


Figure 2. Asymmetric hydrogenation of other ketones: **3**, **4** with $Pd(CF_3CO_2)_2$/(*R,R*)-Me-DuPhos, and **5** with $Pd(CF_3CO_2)_2$/(*S*)-SYNPHOS.

tion of ketone **3** with a NHBz group gave the corresponding alcohol with complete conversion and 74.6% ee, which is

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(11) (a) Bergmeier, S. C.*Tetrahedron* **2000**, *56*, 2561. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (c) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117. (d) Bogevig, A.; Pastor, I. M.; Adolfsson, H. *Chem. Eur. J.* **2004**, *10*, 394. (e) Petra, D. G. I.; Reek, J. N. H.; Handgraaf, J. W.; Meijer, E. J.; Dierkes, P.; Kamer, P. C. J.; Brussee, J.; Schoemaker, H. E.; Van Leeuwen, P. W. N. M. *Chem. Eur. J.* **2000**, *6*, 2818. (f) Atkinson, R. S.; Kelly, B. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1362.
(12) Phthalimide ketones are readily prepared from phthalimide and halide substituted ketone in the presence of potassium carbonate (see Supporting Information).
(13) Ru-Catalyzed asymmetric hydrogenation of α-phthalimide ketones: (a) Lei, A.; Wu, S.; He, M.; Zhang, X. *J. Am. Chem. Soc*. **2004**, *126*, 1626. (b) Hu, A.; Lin, W. *Org. Lett.* **2005**, *7*, 455.
(14) For preparation of complex, see Supporting Information.

(15) **Typical Procedure for the Asymmetric Hydrogenation.** (*R,R*)-Me-DuPhos (1.8 mg, 0.006 mmol) and $Pd(CF_3CO_2)_2$ (1.7 mg, 0.005 mmol) were placed in a Schlenk tube under a nitrogen atmosphere, and degassed anhydrous acetone was added. The mixture was stirred at room temperature for about 1 h. The solvent was removed under vacuum to give the catalyst. This catalyst was taken into a glovebox filled with nitrogen and dissolved in dry TFE (1.2 mL), the catalyst solution was transferred by a syringe to stainless steel autoclave, in which substrate **1** (0.25 mmol) was placed beforehand. The autoclave was stirred under 200−400 psi of hydrogen at oil bath temperature for 12−18 h. The autoclave was cooled to room temperature, and the hydrogen was carefully released. The solvents were removed. Conversion was directly by ^1H NMR spectroscopy. The enantiomeric excess was determined by HPLC after purification on silica gel (hexane/EtOAc/CH_2Cl_2 = 4/1/1). The absolute configuration of **2** was determined by measurement of its optical rotation and comparison to the literature value or by analogue.

lower than with the corresponding α-phthalimide ketones. Hydrogenation of *β*-ketoester **4** gave the corresponding alcohol with complete conversion and 47.9% ee. Interestingly, simple ketone **5** can also be hydrogenated by $Pd(CF_3CO_2)_2$/(*S*)-SYNPHOS to obtain 90% conversion and 51.9% ee.

It is noted that the asymmetric induction sense of the palladium-catalyzed asymmetric hydrogenation of ketones is the same as the corresponding Ru complexes with the same ligand. For example, for hydrogenation of **1a**, $Pd(CF_3CO_2)_2$/(*S*)-MeO-Biphep (entry 9, Table 2) and $RuCl_2$/(*S*)-MeO-Biphep[13a] gave the product with the same *R* configuration.

In conclusion, we have described the highly enantioselective homogeneous hydrogenation of functionalized ketones using a chiral Pd complex in TFE. This is the first example with a Pd/bisphosphines complex as a homogeneous asymmetric hydrogenation catalyst of ketones. This approach will provide principles and insights into the developing area of Pd-catalyzed reaction chemistry. Our ongoing experiments are focused on the asymmetry hydrogenation of other substrates and expanding other Pd-catalyzed asymmetric reactions. The role of TFE[16,17] and the mechanism in this reaction is also under investigation.

Acknowledgment. We are grateful for the financial support from National Science Foundation of China (20302005) and Talent Scientist Program, the Chinese Academy of Sciences.

Supporting Information Available: Specroscopic date, GC, HPLC spectra, and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) TFE as a solvent influences the chemical character of substrates: (a) Teunissen, H. T.; Elsevier, C. J. *Chem. Commun.* **1998**, 1367. (b) Whitfield, H. J.; Griffin, R. J.; Hardcastle, I. R.; Henderson, A.; Meneyrol, J.; Mesguiche, V.; Sayle, K. L.; Golding, B. T. *Chem. Commun.* **2003**, 2802.