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Highly Enantioselective Asymmetric Hydrogenation of α-Phthalimide Ketone: An Efficient Entry to Enantiomerically Pure Amino Alcohols

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Chiral amino alcohol is a key function group in biologically active molecules.[1] Consequently, the construction of this structural motif attracts extensive efforts by organic chemists.[2] Developing highly enantioselective methods to prepare amino alcohols with efficiency remains one of the major challenges. Without any doubt, asymmetric hydrogenation is the most powerful method to make chiral molecules.[3] For example, asymmetric hydrogenation of ketones is regarded as the most successful method to form chiral alcohols.[4] However, there are few successes in ketone hydrogenation with an α-NH_2 group. Very recently, Noyori applied $RuCl_2$-(bisphosphine)(1,2-diamine) complexes, efficient catalysts for reducing unfunctionalized ketones, to the asymmetric hydrogenation of amino ketones in the presence of a strong base.[5] Herein, we describe our highly enantioselective asymmetric hydrogenation of α-phthalimide ketones to form α-phthalimide alcohols, the masked α-primary amino alcohols.

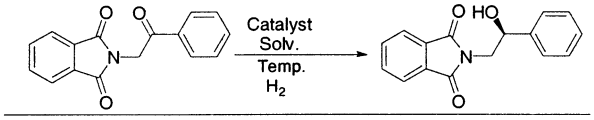
Our initial attempts started with the hydrogenation of *N*-phenacyl-phthalimide using different catalysts, and the results are shown in Table 1. First, high activity and mild conditions were achieved when the [Rh(NBD)(TangPhos)]SbF_6 **1** was chosen as catalyst precursor.[6] Unfortunately, all efforts to try to improve the ee value failed by using catalyst **1**. Catalyst **2** also gave low reactivity and unsatisfactory enantioselectivity. Catalyst **3d** was inactive at room temperature and under 30 psi hydrogen pressure.[7] An unexpected result was observed when we tried to improve the ee by using methanol at 80 °C and under 1500 psi of hydrogen pressure. In this system, the ee value jumped to 90.1% when **3d** was used as the catalyst (Table 1, entry 6). During the process of condition optimization, we observed an interesting solvent-dependent phenomenon. Using EtOH as the solvent, the hydrogenation takes place smoothly in 95.1% ee and 100% conversion (Table 1, entry 11). When other solvents such as toluene, CH_2Cl_2, EtOAc, $ClCH_2CH_2Cl$, and THF (Table 1, entries 7−10) were employed, the reaction was very slow. Using similar alcohol solvents such as methanol, 2-propanol, or *n*-propanol, we observed low reactivity (Table 1, entries 6 and 12).

Due to the advantage of the tunable nature of TunePhos ligand,[8] we were able to further screen the catalysts of our chiral ligand toolbox[9] for hydrogenation. The best result was found by using C_3-TunePhos as ligand, in which 98.5% ee and 100% conversion were obtained (catalyst **3c**). Using MeO−BIPHEP or BINAP as the ligands, we calculated the ee's to be 94.3% and 96.1%, respectively.

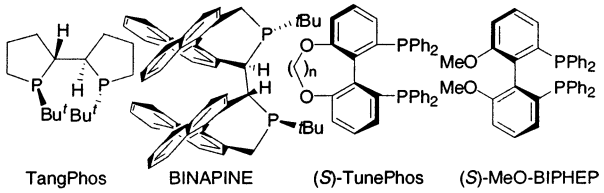
The substrate scope is shown in Table 2. Both electron-deficient and electron-rich aryl ketones can be reduced with high enantioselectivity. The position of substituents is also widely compatible with highly enantioselective reduction. Whether *o*-, *m*-, or *p*-methoxy aryl ketones were hydrogenated, the ee values were higher than 98.5%. In addition, the compatibility of functional groups was examined. Aryl fluorides, chlorides, and even the versatile aryl bromides can be attached in the substrates. Obviously, tolerance of this functional group is useful for synthetic applications. Alkyl ketones and even a simple methyl ketone work well and give high enantioselectivity (Table 2, entries 10 and 11).

Scheme 1 shows an overall picture of a potential synthetic application. The starting materials can be obtained economically, and the reaction can be run on a large scale from inexpensive chloroacetone and phthalimide, providing an almost quantitative yield. Up to 10 000 turnovers have been achieved in over 99% ee in the hydrogenation reaction. The hydrolysis of the phthalimide

Table 1. Asymmetric Hydrogenation of *N*-Phenacyl-phthalimide



Entry	Slov.	Temp.(°C)	H_2 (psi)	Catalyst	*ee*(%)	Conv. (%)
1	CH_2Cl_2	rt	30	**1**	17.0	100
2	CH_2Cl_2	rt	30	**2**	27.0	35
3	CH_2Cl_2	rt	30	**3d**	NA	0
4	MeOH	80	1500	**1**	10.0	100
5	MeOH	80	1500	**2**	29.0	100
6	MeOH	80	1500	**3d**	90.1	29
7	CH_2Cl_2	80	1500	**3d**	NA	0
8	EtOH	80	30	**3d**	NA	0
9	THF	80	1500	**3d**	0	25
10	Toluene	80	1500	**3d**	50.2	11
11	$ClCH_2CH_2Cl$	80	1500	**3d**	0	12
12	EtOAc	80	1500	**3d**	17.3	9
13	EtOH	80	1500	**3d**	95.1	100
14	IPA	80	1500	**3d**	33.7	70
15	EtOH	80	1500	**3a**	91.3	70
16	EtOH	80	1500	**3b**	90.3	72
17	EtOH	80	1500	**3c**	98.5	100
18	EtOH	80	1500	**3e**	95.3	100
19	EtOH	80	1500	**3f**	90.7	100
20	EtOH	80	1500	**4**	94.3	100
21	EtOH	80	1500	**5**	96.1	100



TangPhos BINAPINE (*S*)-TunePhos (*S*)-MeO-BIPHEP

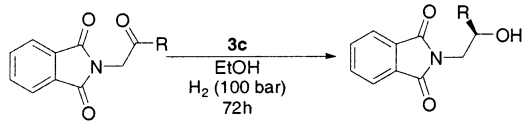
[Rh(NBD)(TangPhos)]SbF_6 **1** [NMe_2H_2][{RuCl(MeO-BIPHEP)}$_2$(μ-Cl)$_3$] **4**

[Rh(NBD)(BINAPINE)]SbF_6 **2** [NMe_2H_2][{RuCl(BINAP)}$_2$(μ-Cl)$_3$] **5**

[NMe_2H_2][{RuCl(*S*-TunePhos)}$_2$(μ-Cl)$_3$] n=1 **3a**; n=2 **3b**; n=3 **3c**; n=4 **3d**; n=5 **3e**; n=6 **3f**;

10.1021/ja039153n CCC: $27.50

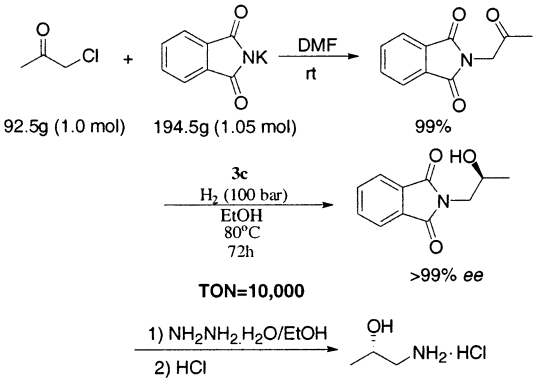
Table 2. Asymmetric Hydrogenation of α-Phthalimide Ketone[a]



entry	R	*T* (°C)	conv (%)	ee (%)[b]
1	*p*-$MeOC_6H_5$	80	100	95.3
2	*p*-$MeOC_6H_5$	60	60	98.5
3	*p*-MeC_6H_5	80	100	>99.0
4	*p*-FC_6H_5	60	100	>99.0
5	*p*-ClC_6H_5	80	100	92.3
6	*p*-ClC_6H_5	60	30	94.0
7	*p*-BrC_6H_5	80	100	>99.0
8	*m*-$MeOC_6H_5$	80	100	>99.0
9	*o*-$MeOC_6H_5$	60	100	>99.0
10	Me	60	100	>99.0
11	Et	80	100	>99.0

[a] The reaction was carried out with 2 mol % Ru catalyst. [b] The ee values were detected via HPLC.

Scheme 1. Highly Enantioselective and Practical Synthesis of 1-Amino-2-propanol

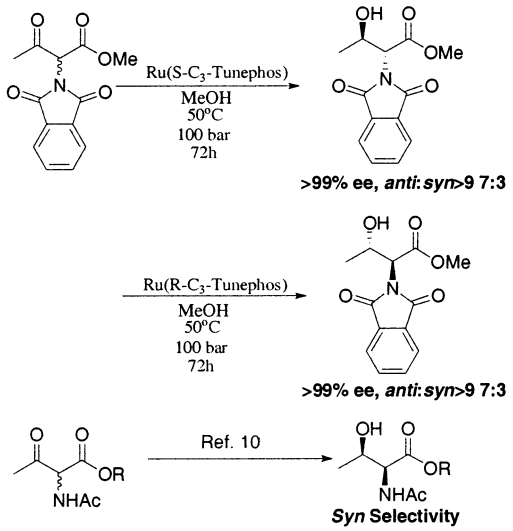


provides the (*S*)-(+)-1-amino-2-propanol (1 g/$25.50, Acros) in the reflux ethanol in the presence of NH_2NH_2 in 98% yield.

The most exciting application for this catalyst system is a dynamically kinetic resolution for the synthesis of threonine (Scheme 2). Using catalyst **3c**, we obtained *allo*-threonine derivative in more than 99% ee and >97:3 dr. Compared with Noyori's system,[10] the syn/anti selectivity was totally reversed. We obtained a ratio of more than 97:3 anti/syn selectivity. Thus, using our catalysts (*R*-C_3-TunePhos and *S*-C_3-TunePhos), both (2*R*,3*R*)-(−)-*allo*- and (2*S*,3*S*)-(+)-*allo*-threonine derivatives can be obtained in high optical purity, in which the *allo*-threonines are more expensive isomers (25 mg/$39 for D-form and 100 mg/$71.80 for L-form, Aldrich) compared with threonine (5 g/$15.80 for D-form and 100 g/$76.50 for L-form, Aldrich). Thus, four isomers of threonine can be selectively obtained by catalyst system choice. To our knowledge, this is the first report of using hydrogenation to achieve high anti configuration of chiral amino alcohols.

In summary, a new type of α-phthalimide ketone was asymmetrically hydrogenated in excellent enantioselectivity. This provides an efficient method to synthesize enantiomerically pure amino alcohols, which is important in synthetic chemistry, medicinal

Scheme 2. High *anti*-Selectivity and Efficient Dynamically Kinetic Resolution Lead the Formation of Optically Pure *allo*-Threonine via Ru-Catalyzed Asymmetric Hydrogenation



chemistry, and bioorganic chemistry. The mechanistic study and further synthetic utilities of this new type of substrate are currently being explored in this lab and will be reported in due course.

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

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