ORGANIC LETTERS

2005
Vol. 7, No. 3
455−458

# Ru-Catalyzed Asymmetric Hydrogenation of α-Phthalimide Ketones and 1,3-Diaryl Diketones Using 4,4′-Substituted BINAPs

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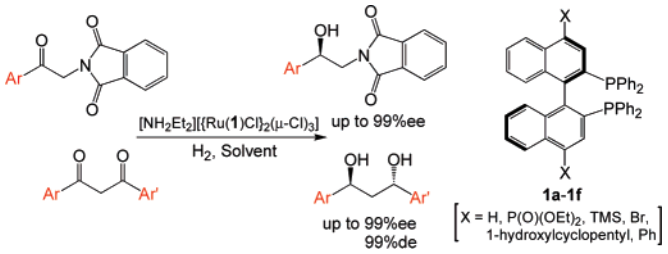
**Received December 8, 2004**

## ABSTRACT




**A family of tunable precatalysts $[NH_2Et_2][\{Ru(4,4'\text{-BINAP})Cl\}_2(\mu\text{-}Cl)_3]$ was synthesized and used for highly enantioselective hydrogenation of phthalimide-protected amino ketones and 1,3-diaryldiketones. The bulky groups on the 4,4′-positions of BINAP were believed to be responsible for the enhancement of enantioselectivity (and diasteroselectivity) in these reactions.**

Since its first introduction by Noyori et al. in the early 1980s, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP, **1a**) has established itself as one of the most widely explored and used chiral ligands in asymmetric synthesis and catalysis, both in academic laboratories and industrial settings.[1] BINAP and its derivatives, notably *p*-TolBINAP and XylBINAP, have been widely used in Ru-, Rh-, and Pd-mediated asymmetric processes including hydrogenation of dehydroamino acid derivatives, functionalized and simple ketones, heterocyclic imine, and functionalized olefin,[2] allylic isomerization,[3] Michael-type conjugate additions,[4] and hydroamination reactions.[5] Seminal work by Noyori et al. has shown that BINAP-type atropisomeric ligands are particularly effective for Ru-catalyzed asymmetric hydrogenation of a variety of functionalized ketones in terms of both high turnover numbers and stereoselectivity. It was however observed that for Ru catalysts based on BINAP-type ligands, much inferior ee's were typically obtained for the substrates with the aryloyl moiety (compared to their alkyloyl counterparts). Although numerous BINAP derivatives have been synthesized over the past couple of decades in order to

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10.1021/ol0474812 CCC: $30.25 
**Published on Web 01/13/2005**

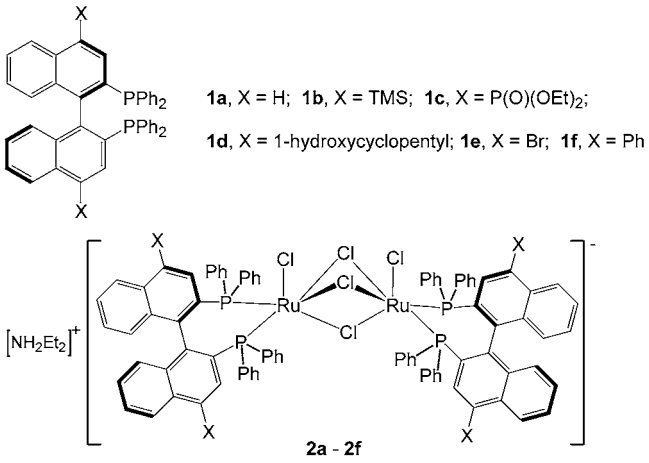
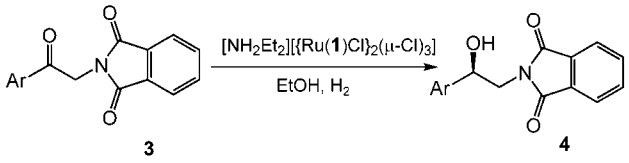



**Figure 1.** Structures of the 4,4′-disubstituted BINAPs (**1a**−**f**) and proposed structures for precatalysts **2a**−**f**.

facilitate the recycling of the asymmetric catalysts for reuse, there have been no reports on modification of the binaphthyl skeleton of BINAP to enhance the stereoselectivity prior to our work. We have recently developed a family of 4,4′-disubstituted BINAPs and used them for highly enantioselective Ru-catalyzed asymmetric hydrogenation of $\beta$-aryl $\beta$-ketoesters and aromatic ketones.[6] X-ray single-crystal structure and molecular modeling studies have shown that bulky substituents on the 4,4′-positions of BINAP can have significant repulsive interactions with the stereo-demanding aryl group of the substrate in the disfavored transition state, thus resulting in enhanced ee over BINAP. We were interested in examining the scope of such 4,4′-substituent effects of BINAP on Ru-catalyzed asymmetric hydrogenation reactions. Herein we wish to report highly enantioselective and diastereoselective asymmetric hydrogenation of protected amino ketones and 1,3-diaryldiketones with Ru catalysts derived from these 4,4′-disubstituted BINAPs. The hydrogenation products of these reactions (chiral amino alcohols upon workup and diols) are key precursors of many important biologically active compounds as well as useful chiral auxiliaries and ligands.[7,8]

4,4′-Disubstituted BINAPs (**1b**−**f**) were synthesized according to our recently published procedures.[6a] The chiral precatalysts $[NH_2Et_2][\{Ru(R\text{-}4,4'\text{-}BINAP)Cl\}_2(\mu\text{-}Cl)_3]$, **2a**−**f**, were synthesized by refluxing a mixture of 4,4′-BINAP, $[NH_2Et_2]Cl$, and $[Ru(benzene)Cl_2]_2$ in toluene for 8 h according to the procedures established by Mashima et al.[9] The resulting brown solids after the removal of organic volatiles were used for asymmetric hydrogenation without further purification.

**Table 1.** Enantiomeric Excess Values (%) for the Asymmetric Hydrogenation of Phthalimide-Protected Amino Ketones[a]




| Ar | 2a | 2b | 2c | 2d | 2e | 2f |
|---|---|---|---|---|---|---|
| **3a** (Ph) | 96.0 | 99.0 | 94.4 | 95.5 | 93.3 | 94.5 |
| **3b** (1-Nap) | 80.0 | 98.4 | 92.4 | 86.7 | 89.4 | 92.3 |
| **3c** (2-Nap) | 94.1 | 97.2 | 94.9 | 94.5 | 90.0 | 92.2 |
| **3d** (4-MeO-Ph) | 91.5 | 95.7 | 92.0 | 86.1 | 85.3 | 90.1 |
| **3e** (4-Me-Ph) | 93.8 | 97.7 | 96.6 | 89.3 | 91.7 | 91.3 |
| **3f** (4-Cl-Ph) | 94.0 | 98.1 | 96.9 | 96.3 | 88.8 | 91.4 |
| **3g** (4-Br-Ph) | 93.6 | 97.9 | 95.6 | 96.0 | 97.2 | 88.7 |

[a] All the reactions were carried out at 80 °C with 1 mol % catalyst and under 1500 psi of hydrogen pressure in 72 h. The ee values were determined by HPLC on a Diacel Chiralcel OJ column. The absolute configurations of the products obtained with (*R*)-**2b**−**f** are identical to those obtained by the $[NH_2Et_2][\{Ru(R\text{-}BINAP)Cl\}_2(\mu\text{-}Cl)_3]$ (**2a**) precatalyst. All conversions were >95% as judged by the integrations of the NMR peaks of crude product.

Owing to the prevalence of chiral amino alcohol functionalities in biologically active molecules and as chiral auxiliaries,[7] much effort has been devoted to the development of efficient methods for the asymmetric synthesis of chiral amino alcohols. Zhang et al. has recently reported an elegant method for the synthesis of chiral amino alcohols via the key step of Ru-catalyzed asymmetric hydrogenation of α-phthalimide ketones.[10] We have examined the asymmetric hydrogenation of a family of phthalimide ketones **3a**−**g** using Ru precatalysts derived from the family of 4,4′-BINAPs **1a**−**f** under the conditions reported by Zhang et al. Complete conversion of **3a** to protected amino alcohol **4a** was observed for all the precatalysts **2a**−**f** under 1500 psi of $H_2$ in EtOH at 80 °C over a period of 72 h (Table 1). The ee values however vary significantly among **2a**−**f**: a high ee value of 96.0% was obtained with BINAP-based percatalyst **2a**, whereas slightly lower ee values were obtained with precatalysts **2c**−**f**. Interestingly, an excellent ee of 99.0% was obtained for the hydrogenation of **3a** with precatalyst **2b**. In comparison, 97.2% ee was obtained for the hydrogenation of **3a** with Ru(**1b**)$(DMF)_2Cl_2$ as the precatalyst.[6a] We thus chose the anionic dinuclear Ru complexes **2a**−**f** as precatalysts for the hydrogenation of other phthalimide-protected amino ketones.

As shown in Table 1, 4,4′-BINAPs with bromo and phenyl substituents (**1e** and **1f**) were inferior to BINAP for most of the α-phthalimide ketone substrates examined. The 4,4′-

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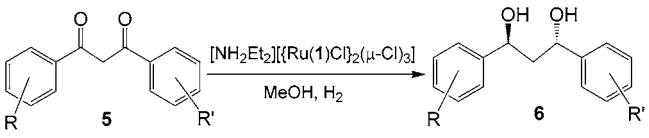
BINAP with 1-hydroxycyclopentyl groups (**1d**) was comparable to BINAP, while the 4,4′-BINAP with diethylphosphonate ester groups (**1c**) performs slightly better than BINAP. Ru precatalyst **2b** derived from 4,4′-$(TMS)_2$-BINAP gave the best results: a variety of α-phthalimide ketone substrates **3b**−**g** were hydrogenated with complete conversion and very high ee values of 95.6−98.4% under 1500 psi of $H_2$ in EtOH at 80 °C over a period of 72 h. This level of enantioselectivity is better than that afforded by BINAP but slightly lower than those reported by Zhang et al. using TunePhos-derived Ru catalysts. Interestingly, the influence of the 4,4′-substituents on BINAP seen here is different from our earlier results on asymmetric hydrogenation of β-aryl β-ketoesters and aromatic ketones.[6] For the asymmetric hydrogenation of β-aryl β-ketoesters and aromatic ketones, the bulky substituents on the 4,4′-positions of BINAP indiscriminatingly led to ee enhancement. The asymmetric hydrogenation of α-phthalimide ketones seems to intricately depend on other factors such as the dihedral angle of the biaryl diphosphines.[10]

Encouraged by the positive 4,4′-effects of **1b** on the asymmetric hydrogenation of α-phthalimide ketones, we examined its utility in the asymmetric hydrogenation of 1,3-diaryl diketones. Asymmetric hydrogenation of 1,3-diketones is one of the simplest and most efficient ways to synthesize enantiopure 1,3-diols, which serve as important chiral synthons.[8] Although there are numerous reports on highly enantioselective hydrogenations of 1,3-dialkyl diketones,[11] the asymmetric hydrogenation of 1,3-diaryl diketones is significantly more challenging with the notable exception of a ferrocene-based chiral phosphine (Taniaphos) reported by Knochel et al.[12−14]

The asymmetric hydrogenation of dibenzoylmethane was first tested with **2a** as the precatalyst. With 0.5 mol % of (*R*)-**2a** in anhydrous methanol, dibenzoylmethane was completely hydrogenated to (*S*,*S*)-enriched 1,3-diphenylpropane-1,3-diol with 46% ee and 88% de under 1500 psi of hydrogen at 50 °C (Table 2). In comparison, both ee's and de's were significantly enhanced when 4,4′-substituted BINAPs were used in place of BINAP. For example, dibenzoylmethane was completely hydrogenated to 1,3-diphenylpropane-1,3-diol in 99% ee and 99% de with **2b** and in 99% ee and 94% de with **2c**, respectively.

**Table 2.** Asymmetric Hydrogenation of 1,3-Diaryl Diketones[a]




| (R, R′) | cat. | ee % | de % | cat. | ee % | de % |
|---|---|---|---|---|---|---|
| **5a** (H, H) | **2a** | 46 | 88 | **2b** | >99 | >99 |
| | | | | **2c** | 99 | 94 |
| **5b** (4-Me, 4′-Me) | **2a** | 50 | 83 | **2b** | 99 | 94 |
| **5c** (3-Me, 3′-Me) | **2a** | 38 | 76 | **2b** | >99 | 95 |
| **5d** (2-Me, 2′-Me) | **2a** | 80 | 90 | **2b** | >99 | >99 |
| **5e** (4-Cl, 4′-Cl) | **2a** | 46 | 73 | **2b** | 99 | 92 |
| **5f** (4-Me, H) | **2a** | 50 | 80 | **2b** | >99 | 97 |
| **5g** (4-Cl, H) | **2a** | 45 | 80 | **2b** | >99 | 97 |
| **5h** (4-Me, 4′-Cl) | **2a** | 43 | 71 | **2b** | >99 | 99 |

[a] All of the reactions were carried out at 50 °C with 0.5 mol % catalyst under 1500 psi of hydrogen in 40 h, and the ee values were determined by HPLC on a Diacel Chiralcel OD or OJ or Chiralpak AD column (see Supporting Information). All conversions were >95% as judged by the integrations of the NMR spectra for the crude products. For unsymmetrical diols, de stands for the excess of homochiral isomers over heterochiral isomers.

We have also compared the effectiveness of **2a** and **2b** in the asymmetric hydrogenation of several symmetrical and unsymmetrical 1,3-diaryl diketones **5b**−**h** under identical conditions. As shown in Table 2, precatalyst **2b** gave ee's and de's much higher than those of **2a** for all of the symmetrical and unsymmetrical 1,3-diaryl diketones. The ee's are 99% or higher for all of the substrates with different substitution patterns on the aryl group. The *para*-substituents however seem to slightly deteriorate the de's in these reactions. When the hydrogenation of **5b** with precatalyst **2b** was stopped after 5 h, the reaction mixture contained 60 mol % of hydroxyketone intermediate (93% ee), 35 mol % of diol 6**b** (98% ee, 92% de), and <5 mol % of diketone **2b**. This control experiment seems to indicate that the slightly low de's observed for the *para*-substituted diketones are a result of the lower enantio-differentiation during the diketone hydrogenation to the hydroxyketone intermediate (but not during the hydrogenation of hydroxyketones to diols). To our knowledge, this is the first Ru catalyst for the hydrogenation of a broad spectrum of 1,3-diaryl diketones with excellent ee's and de's.

Given the structural similarity of 1,3-diaryl diketone and β-aryl β-ketoester, we believe that the ee enhancement of this reaction by the bulky 4,4′-substituents on BINAP occurs via a similar mechanism to the asymmetric hydrogenation of β-aryl β-ketoester. Molecular modeling using PC Spartan indeed shows that the aryl groups of both Ru-coordinated 1,3-diaryl diketones and hydroxyketone substrates experience significant repulsive interactions with the bulky TMS groups on the 4,4′-positions of **1b** in their disfavored transition states (see Supporting Information).

In summary, we have successfully applied 4,4′-substituted BINAPs in the asymmetric hydrogenation of protected amino ketones and 1,3-diaryl diketones. By taking advantage of bulky 4,4′-substituents on the BINAP moiety, excellent ee's

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(13) ,3-Diaryl diketones were reduced by sodium borohydride with excellent ee's but low de's with chiral ketoiminato cobalt complexes as catalysts. See: Yamada, T.; Nagata, T.; Sugi, K. D.; Yorozu, K.; Ikeno, T.; Ohtsuka, Y.; Miyazaki, D.; Mukaiyama, T. *Chem. Eur. J.* **2003**, *9*, 4485.

(14) ,3-Diaryl diketones have also been successfully reduced to chiral 1,3-diols by Ru-catalyzed transfer hydrogenation reactions developed by Ikariya et al. See: (a) Watanabe, M.; Murata, K.; Ikariya, T. *J. Org. Chem.* **2002**, *67*, 1712. (b) Cossy, J.; Eustache, F.; Daiko, P. I. *Tetrahedron Lett.* **2001**, *42*, 5005.

(and de's) were obtained. Together with our previous work on Ru-catalyzed asymmetric hydrogenation of aromatic ketones and $\beta$-aryl $\beta$-ketoesters, the positive 4,4′-substituent effects on BINAP-derived Ru catalysts are now firmly established.

**Acknowledgment.** We thank NSF (CHE-0208930) for financial support. W.L. is an A.P. Sloan Fellow, a Beckman Young Investigator, a Cottrell Scholar of Research Corp, and a Camille Dreyfus Teacher-Scholar.

**Supporting Information Available:** Detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0474812