ORGANIC LETTERS

2002
Vol. 4, No. 25
4495−4497

# Highly Enantioselective Hydrogenation of Enol Acetates Catalyzed by Ru−TunaPhos Complexes

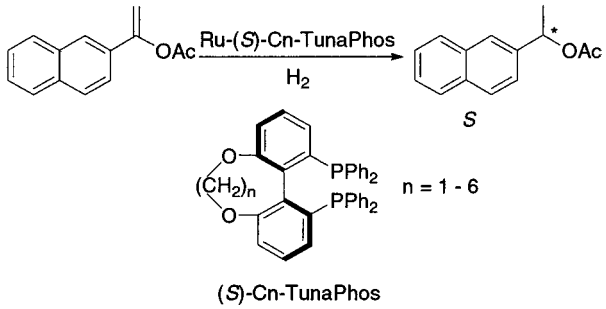
**Shulin Wu, Weimin Wang, Wenjun Tang, Min Lin, and Xumu Zhang***

*Department of Chemistry, The Pennsylvania State University, 152 Davey Laboratory, University Park, Pennsylvania 16802*

*xumu@chem.psu.edu*

**Received October 1, 2002**

## ABSTRACT




**The chiral disphosphines with tunable dihedral angles (TunaPhos) have been used for asymmetric hydrogenation of enol acetates and dihedral-angle-dependent enantioselectivities were observed. C2-TunaPhos has been proved to be effective for Ru-catalyzed asymmetric hydrogenation of electron-deficient and other enol acetates.**

Catalytic asymmetric synthesis presents one of most powerful methods for accessing a wide range of enantiomerically enriched compounds. Design and synthesis of chiral phosphine ligands play a central role for the development of highly enantioselective transition metal-catalyzed asymmetric reactions.[1] Conformationally rigid and yet tunable ligands are often desired for achieving high enantioselectivities.[2] However, there is no general solution in dealing with the many challenging transition metal-catalyzed asymmetric transformations since enantioselectivities are often substrate dependent. In fact, subtle changes in conformational, steric, and or electronic properties of the chiral ligands can often lead to dramatic variation of reactivity and enantioselectivity. For atropisomeric biaryl diphosphines, a small variation of the dihedral angle of the ligands can have a significant impact on the reactivity and selectivity of reactions.[3]

Although atropisomeric biaryl diphosphines such as BINAP,[1,4] BIPHEMP,[1,5] and MeO−BIPHEP[1,5] have been used effectively as ligands for many asymmetric catalytic reactions, they are still not efficient for certain substrates. A major reason is the flexible dihedral angle of these ligands, since

(1) (a) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH: New York, 2000. (b) Jacobson, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis I−III*; Springer: New York, 1999. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994.

(2) (a) Zhou, Y.; Tang, W.; Wang, W.; Li, W.; Zhang, X. *J. Am. Chem. Soc*. **2002**, *124*, 4952. (b) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612. (c) Tang, W.; Chi, Y.; Zhang, X. *Org. Lett*. **2002**, *4*, 1695. (d) Li, W.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 5871 and references cited therein.

(3) (a) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal*. **2001**, *343*, 264. (b) Casey, C. P.; Whiteker, G. T.; Melville, M. G.; Petrovich, L. M.; Gavney, J. A.; Powell. D. R. *J. Am. Chem. Soc*. **1992**, *114*, 5535. (c) Casey, C. P.; Whiteker, G. T. *Isr. J. Chem*. **1990**, *30*, 299. (d) Casey, C. P.; Whiteker, G. T. *J. Org. Chem*. **1990**, *55*, 1394.

(4) (a) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008. (b) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

(5) (a) Schmid, R.; Broger, E. A.; Cereghtti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Muller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem*. **1996**, *68*, 131. (b) Schmid, R.; Foricher, J.; Cereghtti, M.; Schonholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370. (c) Schmid, R.; Cereghtti, M.; Heiser, B.; Schonholzer, P.; Hansen, H.-J. *Helv. Chim. Acta* **1988**, *71*, 897.

10.1021/ol027010k CCC: $22.00 
**Published on Web 11/13/2002**

the sp2−sp2 rotation in these biaryl ligands causes only small energy change within a wide range of dihedral angle. We have recently developed a novel class of diphosphine ligands (Cn-TunaPhos, $n = 1-6$) (Figure 1)[6] with tunable dihedral

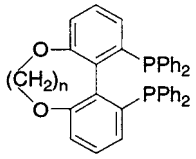
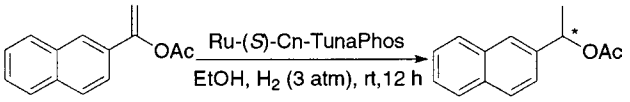



**Figure 1.** C*n*-TunaPhos, $n = 1-6$.

angles by introducing a bridge with variable length to link the chiral atropisomeric biaryl groups. Thus, the sp2−sp2 rotation in these biaryl ligands is restricted. *The interesting point is that each of the ligands adopts a small change of dihedral angle of the chiral backbone*. These ligands allow us to systematically study the influence of dihedral angle of atropisomeric biaryl diphosphines on the reactivity and selectivity of asymmetric reactions. As a result, excellent ligands with high reactivity and enantioselectivity for particular substrates could be found. We have previously demonstrated that TunaPhos are excellent ligands for some asymmetric reactions.[6,7] For example, in Ru-catalyzed asymmetric hydrogenation of $\beta$-keto esters, C4-TunaPhos has shown the best enantioselectivity (up to 99% ee) among the TunaPhos ligands. To further expand the applications of the TunaPhos ligands in asymmetric catalysis, we herein report our recent studies on asymmetric hydrogenation of enol acetates catalyzed by Ru−TunaPhos complexes.

Asymmetric hydrogenation of readily accessible enol acetates is an attractive alternative to direct hydrogenation of unfunctionalized ketones. An advantage of enol acetate substrates is their chelation through secondary donor group.This chelation is important to achieve high enantioselectivity in hydrogenation. Good to excellent enantioselectivites have been achieved upon asymmetric hydrogenation of some cyclic and acyclic enol esters with Rh−phosphine complexes.[8] In contrast, hydrogenation of enol acetates employing Ru-chiral phosphine system is rarely mentioned in the literature.[9] We initiated this study by choosing 1-(2-naphthyl)-1-(acetyloxy)ethylene[10] as the model substrate to screen the reaction conditions. The anionic dinuclear ruthenium (II) complexes of $[NH_2Me_2][\{RuCl((S)\text{-}Cn\text{-}TunaPhos)\}_2(\mu\text{-}Cl)_3]$ ($n = 1-6$) were prepared according to the literature method[11] and used as the catalysts. The reactions were carried out in ethanol at room temperature under 3 atm of hydrogen pressure with a substrate/Ru ratio of 100:1. As shown in Table 1, the Ru−TunaPhos catalysts are generally active and

**Table 1.** Ligand Screening for Ru-Catalyzed Hydrogenation of Enol Acetate




| entry[a] | ligand | dihedral angle[b] (deg) | ee[c] (%) |
|---|---|---|---|
| 1 | C1 | 60 | 95.9 |
| 2 | C2 | 74 | 95.9 |
| 3 | C3 | 77 | 92.1 |
| 4 | C4 | 88 | 88.9 |
| 5 | C5 | 94 | 91.9 |
| 6 | C6 | 106 | 92.3 |

[a] $[NH_2Me_2][\{RuCl[(S)\text{-}Cn\text{-}TunaPhos]\}_2(\mu\text{-}Cl)_3]$ were used as catalysts; substrate/Ru = 100:1; all reactions were complete in >99% conversion. [b] Calculated dihedral angles of C*n*-TunaPhos from CAChe MM2 program.[6] [c] Enantiomeric excesses were determined by chiral GC using a Supelco chiral select 1000 (0.25 mm × 30 m) column; the configuration of the product is *S*.

the reactions were complete in all cases. The obtained enantioselectivities are particularly interesting. *C1- and C2-TunaPhos possessing smaller dihedral angles gave high enantiomeric excesses (both 95.9%).* The enantioselectivity dropped to 92.1% ee with C3−TunaPhos and reached the lowest (88.9% ee) with C4-TunaPhos. Further increase of the dihedral angles led to the increase of enantioselectivities to 91.6% ee with C5-TunaPhos and 92.3% ee with C6-TunaPhos. This trend is in contrast to our previous observations on hydrogenation of $\beta$-ketoesters, where C4-TunaPhos showed the best ee.[6] Although it is still unclear why the TunaPhos ligands provide different trends of ees in the two types of reactions, the phenomenon indicates that different reactions may require diphosphines with different dihedral angles. These results, on the other hand, also reflect the important design of our TunaPhos ligands.

Further experiments with C1 and C2-TunaPhos ligands revealed a strong solvent effect in hydrogenation of 1-(2-naphthyl)-1-(acetyloxy)ethylene (Table 2). The best ee (97.7%) was achieved when a mixture of ethanol/$CH_2Cl_2$ (4:1) was used as the solvent and the Ru−C2-TunaPhos complex was employed as the catalyst (entry 2). This result is higher than those obtained with the Rh−PennPhos system

(6) Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 6223.

(7) Lei, A.; He, M.; Wu, S.; Zhang, X. *Angew. Chem., Int. Ed.* **2002,** *41*, 3457.

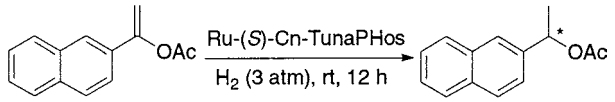
(8) For selected examples of asymmetric hydrogenations of simple enol acetates, see: (a) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 3489. (b) Jiang, Q.; Xiao, D.; Zhang, Z.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **1999**, *38*, 516 and the references cited. (c) Boaz, N. W. *Tetrahedron Lett.* **1998**, *39*, 5505. (d) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (e) Koenig, K. E.; Bachman, G. L.; Vineyard, B. D. *J. Org. Chem.* **1980**, *45*, 2362.

(9) For asymmetric hydrogenation of 1-phenyl-1-(acetyloxy)ethylene with Ru−BINAP complex, see: Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takaya, H. *J. Org. Chem.* **1995**, *60*, 357. For asymmetric hydrogenation of 1,1,1-trifluoroalkan-2-one enol acetates, see: Kuroki, Y.; Asada, D.; Sakamaki, Y.; Iseki, K. *Tetrahedron Lett.* **2000**, *41*, 4603.

(10) For the synthesis of enol acetates, see: Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; p 743.

(11) (a) Mashima, K.; Nakanura, T.; Matsuo, Y.; Tani, K. *J. Organomet. Chem.* **2000**, *607*, 51. (b) Ohta, T.; Tonomura, Y.; Nazaki, K.; Takaya, H.; Mashima, K. *Organometallics* **1996**, *19*, 1521. (c) Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922.

**Table 2.** Optimization of Reaction Conditions for Ru-Catalyzed Hydrogenation of Enol Acetate



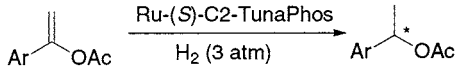

| entry[a] | ligand | solvent | conversion (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | C1 | EtOH/$CH_2Cl_2$[b] | >99 | 92.7 |
| 2 | C2 | EtOH/$CH_2Cl_2$[b] | >99 | 97.7 |
| 3 | C3 | MeOH | 30.3 | 71.0 |
| 4 | C4 | MeOH/$CH_2Cl_2$[b] | 31.4 | 75.3 |
| 5 | C5 | EtOH/$CH_2Cl_2$[b] | >99 | 94.0[d] |
| 6 | C6 | EtOH/$CH_2Cl_2$[b] | >99 | 95.8[e] |

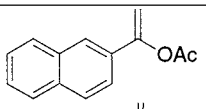
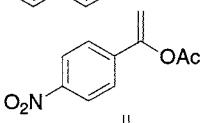
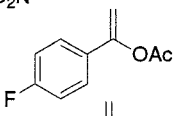
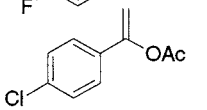
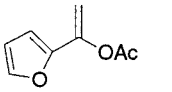
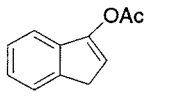
[a] $[NH_2Me_2][\{RuCl[(S)\text{-}Cn\text{-}TunaPhos]\}_2(\mu\text{-}Cl)_3]$ were used as catalysts; substrate/Ru = 100:1. [b] v/v = 4:1. [c] Enantiomeric excesses were determined by chiral GC using a Supelco chiral select 1000 (0.25 mm × 30 m) column; the configuration of the product is *S*. [d] The reaction was carried out under a $H_2$ pressure of 10 atm. [e] The reaction was carried out at 50 °C.

(80.9% ee) [8b] and Rh−Et-KetalPhos system (94.5% ee).[8a] When methanol was used as the solvent, both the reactivities and the enantioselectivities decreased dramatically (entries 3 and 4). The hydrogenation did not proceed in pure $CH_2Cl_2$, THF, toluene, and even alcoholic $CF_3CF_2OH$. In addition, small pressure and temperature effects were also observed (entries 5 and 6).

With the optimized ligand and reaction conditions, several other enol acetates were examined for hydrogenation with the Ru−C2-TunaPhos catalyst (Table 3). Hydrogenation of 1-aryl-(acetyloxy) ethylenes with an electron-withdrawing substituent on the phenyl ring gave excellent enantioselectivities (entries 2, 3, and 5). For example, hydrogenation of 1-(4-nitrophenyl)-1-(acetyloxy)ethylene afforded 100% conversion and 96.6% ee, which was higher than that observed with Rh−BPE system (90% ee).[8d] To our surprise, hydrogenation of relatively electron-rich substrates such as 1-phenyl-1-(acetyloxy) ethylene and 1-(4-methoxyphenyl)-1-(acetyloxy)ethylene did not occure under the present reaction conditions. The starting materials were recovered along with a small amount of hydrogenolysis products. On the other hand, an electron-rich enol acetate bearing a furyl group gave a high ee (93.1%) albeit with a moderate conversion. This result indicates that a secondary interaction between the oxygen atom in furan and the catalyst might play a role in this transformation. Interestingly, over 99% ee was also achieved upon hydrogenation of enol acetate derived from 1-indanone with a prolonged reaction time and at an elevated temperature (entry 9), which was comparable to the best result reported in the literature.[8b]

**Table 3.** Hydrogenation of Enol Acetates Catalyzed by a Ru−C2-TunaPhos System




| entry[a] | substrate | time (h) | conversion (%) | ee (%)[b] |
|---|---|---|---|---|
| 1 |  | 12 | >99 | 97.7 |
| 2 |  | 12 | >99 | 96.6 |
| 3 |  | 12 | >99 | 97.0 |
| 4 |  | 12 | 55.0 | 94.4 |
| 5 | | 48 | >99 | 96.8 |
| 6 |  | 12 | 42.4 | 93.1 |
| 7 |  | 12 | 5.0 | 89.6 |
| 8 | | 12 | 72.3 | 99.0[c] |
| 9 | | 48 | 97.9 | 99.2[c] |

[a] $[NH_2Me_2][\{RuCl[(S)\text{-}C2\text{-}TunaPhos]\}_2(\mu\text{-}Cl)_3]$ was used as the catalyst and EtOH/$CH_2Cl_2$ (4:1) as the solvent; substrate/Ru = 100:1. [b] Enantiomeric excesses were determined by chiral GC using a Supelco chiral select 1000 (0.25 mm × 30 m) column; the configuration of the products is *S*. [c] The reaction was carried out at 50 °C.

In conclusion, a series of chiral diphosphines with tunable dihedral angles have been used for asymmetric hydrogenation of enol acetates. C2-TunaPhos has been proved to be effective for Ru-catalyzed asymmetric hydrogenation of electron-deficient and other enol acetates. Further investigations of other catalytic asymmetric reactions with the TunaPhos ligands are underway and progress will be disclosed in due time.

**Acknowledgment.** This work was supported by the National Institute of Health. We acknowledge Johnson Matthey for a gift of precious metals.

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

OL027010K