

Asymmetric Hydrogenation of Alkynyl Ketones with the η^6 -Arene/TsDPEN–Ruthenium(II) Catalyst

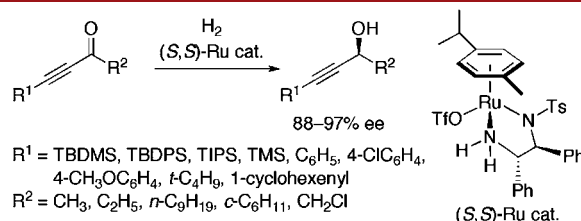
Noriyoshi Arai,[†] Hironori Satoh,[†] Noriyuki Utsumi,[‡] Kunihiro Murata,[‡] Kunihiro Tsutsumi,[‡] and Takeshi Ohkuma^{*†}

Division of Chemical Process Engineering and Frontier Chemistry Center, Faculty of Engineering, Hokkaido University, Sapporo, Hokkaido 060-8628, Japan, and Central Research Laboratory, Technology and Development Division, Kanto Chemical Co., Inc., Soka, Saitama 340-0003, Japan

ohkuma@eng.hokudai.ac.jp

Received May 1, 2013

ABSTRACT



Enantioselective hydrogenation of alkynyl ketones catalyzed by Ru(OTf)(TsDPEN)(η^6 -*p*-cymene) (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) affords the propargylic alcohols in up to 97% ee. The alkynyl moieties are left intact in most cases. The reaction can be conducted with a substrate-to-catalyst molar ratio as high as 5000 under 10 atm of H₂. The mode of enantioselection is elucidated with the transition state models directed by the CH/ π attractive interaction between the substrate and the catalytic species.

Optically active propargylic alcohols are synthetically important compounds that can be transformed to a variety of chiral molecules.¹ Asymmetric hydrogenation of alkynyl ketones **1** is one of the most direct and atom-efficient reactions to produce these useful compounds. To our knowledge, however, there have been no successful reports of this reaction,^{2,3} probably due to three hardly dissolved problems (Figure 1). (1) Chemoselective hydrogenation of the carbonyl groups over the alkynyl moieties activated by the electron-withdrawing acyl functionalities is difficult.

The alkynyl groups of propargylic alcohols, the desired product, are also highly reactive under conventional hydrogenation conditions.⁴ (2) Many alkynyl ketones are significantly labile under basic and/or reductive conditions, and the decomposed compounds tend to inhibit the catalyst performance. (3) Differentiation between the similarly sized alkyl and alkynyl groups is hardly achieved, resulting in insufficient enantioselectivity.

We have studied asymmetric hydrogenation of ketones catalyzed by the η^6 -arene/TsDPEN–Ru(II) (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine)⁵ and MsDPEN–Cp*Ir(III) (MsDPEN = *N*-(methanesulfonyl)-1,2-diphenylethylenediamine)⁶ complexes.⁷ The catalytic

[†] Hokkaido University

[‡] Kanto Chemical Co., Inc.

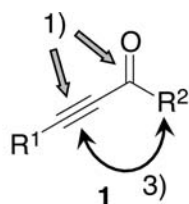
(1) (a) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995. (b) Pu, L. *Tetrahedron* **2003**, *59*, 9873–9886. (c) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095–4105. (d) Lu, G.; Li, Y.-M.; Li, X.-S.; Chan, A. S. C. *Coord. Chem. Rev.* **2005**, *249*, 1736–1744. (e) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963–983.

(2) For catalytic asymmetric borane reduction, see: (a) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938–10939. (b) Parker, K. A.; Ledebner, M. W. *J. Org. Chem.* **1996**, *61*, 3214–3217. (c) Bach, J.; Berenguer, R.; Garcia, J.; Loscertales, T.; Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 9021–9025.

(3) For asymmetric transfer hydrogenation, see: Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.

(4) See for example: (a) Rylander, P. *Catalytic Hydrogenation in Organic Synthesis*; Academic Press: New York, 1979; pp 13–30. (b) Takaya, H.; Noyori, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, pp 443–469. (c) Kluwer, A. M.; Elsevier, C. J. In *Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, 2007; Vol. 1, pp 375–411.

(5) (a) Ohkuma, T.; Utsumi, N.; Tsutsumi, K.; Murata, K.; Sandoval, C.; Noyori, R. *J. Am. Chem. Soc.* **2006**, *128*, 8724–8725. (b) Ohkuma, T.; Tsutsumi, K.; Utsumi, N.; Arai, N.; Noyori, R.; Murata, K. *Org. Lett.* **2007**, *9*, 255–257.



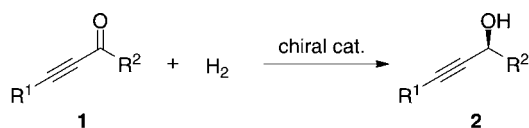
- 1) Chemoselectivity problem
hydrogenation of carbonyl groups over
alkynyl moieties
- 2) Stability problem
lability under basic and/or reductive conditions
- 3) Enantioselectivity problem
discrimination between the alkyl and
alkynyl groups

Figure 1. Problems in the realization of enantioselective hydrogenation of alkynyl ketones **1**.

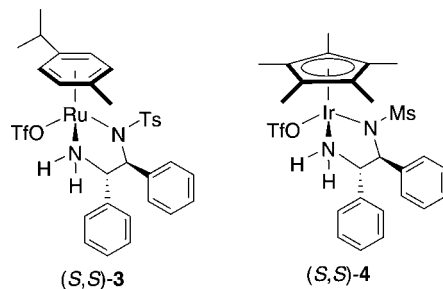
reaction proceeds under neutral to slightly acidic conditions. A series of base-labile ketones, including α -chloro and α -hydroxy ketones^{5b,6a} as well as aromatic heterocyclic ketones,^{5a,6b} was smoothly hydrogenated with high enantioselectivity. We expected that the features of these catalysts would meet the requirements for the asymmetric hydrogenation of alkynyl ketones **1**.

Asymmetric hydrogenation of 4-(*tert*-butyldimethylsilyl)-but-3-yn-2-one (**1a**, 1.54 mmol, Scheme 1) with Ru(OTf)-[(*S,S*)-TsDPEN](η^6 -*p*-cymene) [(*S,S*)-**3**, 1.5 μ mol, substrate-to-catalyst molar ratio (S/C) = 1000] in methanol (4.8 mL) under 10 atm of H₂ at 50 °C was completed in 15 h to afford the *S* propargylic alcohol **2a** in 97% ee (Table 1, entry 1). The reaction with an S/C of 5000 under 50 atm of H₂ for 40 h gave **2a** in 95% ee quantitatively (entry 2). The silylated propargylic alcohols are useful precursors of chiral allenylmetal reagents.⁹ The isoelectronic complex Cp*Ir-(OTf)[(*S,S*)-MsDPEN] [(*S,S*)-**4**], which efficiently catalyzes the asymmetric hydrogenation of α -hydroxy ketones and aromatic heterocyclic ketones,⁶ exhibited relatively lower reactivity and enantioselectivity for this reaction (entry 3). When the reaction was not completed, the recovered ketone contained a small amount of the dimethyl acetal. The hydrogenation of the ethyl and *n*-nonyl ketones, **1b** and **1c**, with the Ru complex **3** was somewhat slower than that of the methyl ketone **1a**, so that a condition of 20 atm of H₂ was required to achieve a high yield of >90% in 15 h (entries 4 and 5). The high level of enantioselectivity (>95%) was maintained. The cyclohexyl ketone **1d**, a secondary alkyl ketone, was smoothly converted to the alcohol **2d** in 96%

Scheme 1. Asymmetric Hydrogenation of Alkynyl Ketones **1**



- | | |
|--|---|
| a: R ¹ = TBDMS, R ² = CH ₃ | h: R ¹ = TIPS, R ² = CH ₃ |
| b: R ¹ = TBDMS, R ² = C ₂ H ₅ | i: R ¹ = TMS, R ² = <i>n</i> -C ₉ H ₁₉ |
| c: R ¹ = TBDMS, R ² = <i>n</i> -C ₉ H ₁₉ | j: R ¹ = C ₆ H ₅ , R ² = CH ₃ |
| d: R ¹ = TBDMS, R ² = <i>o</i> -C ₆ H ₁₁ | k: R ¹ = 4-ClC ₆ H ₄ , R ² = CH ₃ |
| e: R ¹ = TBDMS, R ² = C ₆ H ₅ | l: R ¹ = 4-CH ₃ OC ₆ H ₄ , R ² = CH ₃ |
| f: R ¹ = TBDMS, R ² = CH ₂ Cl | m: R ¹ = <i>t</i> -C ₄ H ₉ , R ² = CH ₃ |
| g: R ¹ = TBDPS, R ² = CH ₃ | n: R ¹ = 1-cyclohexenyl, R ² = CH ₃ |



ee under the regular conditions (entry 6). Interestingly, the degree and sense of enantioselectivity were consistent through the reaction of **1a–1d**, although the relative size of R² toward the alkynyl moiety varied in these substrates. The reaction rate and the enantioselectivity were significantly decreased in the hydrogenation of the phenyl ketone **1e** (entry 7). The hydrogenation of α -chloro ketone **1f** required a lower temperature (30 °C) and a larger catalyst loading (S/C = 200) to achieve complete conversion; these conditions yielded the chlorohydrin **2f** in 96% ee.^{2a,10} The chloro-substituent did not affect the enantioselection. The chlorohydrin **2f** is known to be converted to the chiral alkynyl epoxide.¹⁰

The *tert*-butyldiphenylsilyl (TBDPS) ethynyl and the triisopropylsilyl (TIPS) ethynyl ketones, **1g** and **1h**, were also quantitatively hydrogenated at an S/C of 1000 under the regular conditions to give the propargylic alcohols **2g** and **2h** in 95% ee and 96% ee, respectively (Table 1, entries 9 and 10). The hydrogenation of trimethylsilyl (TMS) ethynyl ketone **1i** did not complete with an S/C of 200, although the level of enantioselectivity remained high (entry 11). The lower conversion may have been due to inhibition of the desilylated compounds formed in the reaction.¹¹ The phenyl ethynyl ketone **1j** was hydrogenated with an S/C of 200 to afford **2j** in 78% yield and in 92% ee accompanied by 0.7% of the 1,4-reduction product (*Z*)-4-phenyl-3-buten-2-one (entry 12). The hydrogenation of 4'-Cl and 4'-CH₃O substituted phenyl ethynyl ketones, **1k** and **1l**, also afforded the propargylic alcohols **2j** and **2k** in high yield with the 1,4-reduction products in 3% and

(6) (a) Ohkuma, T.; Utsumi, N.; Watanabe, M.; Tsutsumi, K.; Arai, N.; Murata, K. *Org. Lett.* **2007**, *9*, 2565–2567. (b) Utsumi, N.; Tsutsumi, K.; Watanabe, M.; Murata, K.; Arai, N.; Kuroki, N.; Ohkuma, T. *Heterocycles* **2010**, *80*, 141–147.

(7) Review: Ohkuma, T. *Proc. Jpn. Acad. Ser. B* **2010**, *86*, 202–219.

(8) This complex was prepared according to the previously reported method; see ref 5. TfO[−] = trifluoromethanesulfonate.

(9) See for example: (a) Marshall, J. A.; Eidam, P.; Eidam, H. S. *J. Org. Chem.* **2006**, *71*, 4840–4844. (b) Brawn, R. A.; Panek, J. S. *Org. Lett.* **2007**, *9*, 2689–2692. (c) Marshall, J. A. *J. Org. Chem.* **2007**, *72*, 8153–8166.

(10) Schubert, T.; Hummel, W.; Müller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 634–637.

(11) The ethynyl ketone (**1**: R¹ = H) was not hydrogenated with the Ru complex **3**.

Table 1. Asymmetric Hydrogenation of Alkynyl Ketones **1** with Chiral Ru or Ir Catalyst^a

entry	1	cat.	S/C ^b	H ₂ , atm	% yield ^c	% ee ^d
1	1a	3	1000	10	94	97
2 ^e	1a	3	5000	50	96	95
3	1a	4	1000	10	73	93
4	1b	3	1000	20	91	95
5	1c	3	1000	20	94	96
6	1d	3	1000	10	94	96
7	1e	3	100	10	16	9
8 ^f	1f	3	200	10	94	96
9	1g	3	1000	10	98	95
10	1h	3	1000	10	98	96
11	1i	3	200	10	63	93
12	1j	3	200	10	78	92
13	1k	3	200	10	92	88
14	1l	3	200	10	88	94
15	1m	3	200	20	61 ^g	89
16	1n	3	200	10	78	95

^a Unless otherwise stated, the reactions were conducted using 0.3–1.5 mmol of **1** in CH₃OH containing (*S,S*)-**3** or **4** under H₂ at 50 °C for 15–24 h. ^b Substrate-to-catalyst molar ratio. ^c Isolated yield. ^d Determined by chiral GC or HPLC analysis of **2** or their derivatives. See the Supporting Information for details. ^e This reaction using 8.46 mmol of **1a** was conducted for 40 h. ^f Reaction at 30 °C. ^g A small amount (ca. 4–5%) of impurity was included.

1% yields, respectively (entries 13 and 14). The stronger electron-donating ability of the 4'-substituent appeared to increase the enantioselectivity (**2k**: 4-Cl, 88% ee; **2j**: 4-H, 92% ee; **2l**: 4-CH₃O, 94% ee). The *tert*-butyl ethynyl ketone **1m** was hardly reducible, so that **2m** in 89% ee was obtained in 61% yield with 4% of the 1,4-reduced compound and undefined products (ca. 4–5%) under 20 atm of H₂ at an S/C of 200 (entry 15). The reaction of 1'-cyclohexenyl ethynyl ketone **1n** selectively afforded the alcohol with an ene-yne moiety in 95% ee (entry 16). No diene compounds were observed.

Previous mechanistic studies on the asymmetric hydrogenation of acetophenone, a simple aromatic ketone, with the Ru catalyst **3** revealed that the active RuH(TsDPEN)-(η^6 -*p*-cymene) reduces the ketone in the catalytic cycle.^{5a,12,13} The reaction of alkynyl ketones using the Ru catalyst **3** appears to proceed through the same reaction mechanism

(12) (a) Sandoval, C. A.; Ohkuma, T.; Utsumi, N.; Tsutsumi, K.; Murata, K.; Noyori, R. *Chem.—Asian J.* **2006**, *1*–2, 102–110. (b) Sandoval, C. A.; Bie, F.; Matsuoka, A.; Yamaguchi, Y.; Naka, H.; Li, Y.; Kato, K.; Utsumi, N.; Tsutsumi, K.; Ohkuma, T.; Murata, K.; Noyori, R. *Chem.—Asian J.* **2010**, *5*, 806–816.

(13) For mechanistic studies of asymmetric transfer hydrogenation of ketones with chiral Ru catalysts, see: (a) Haack, K. J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285–288. (b) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580–9588. (c) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466–1478. (d) 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*, 2818–2829. (e) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931–7944. (f) Yamakawa, M.; Yamada, I.; Noyori, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2818–2821. (g) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237–248.

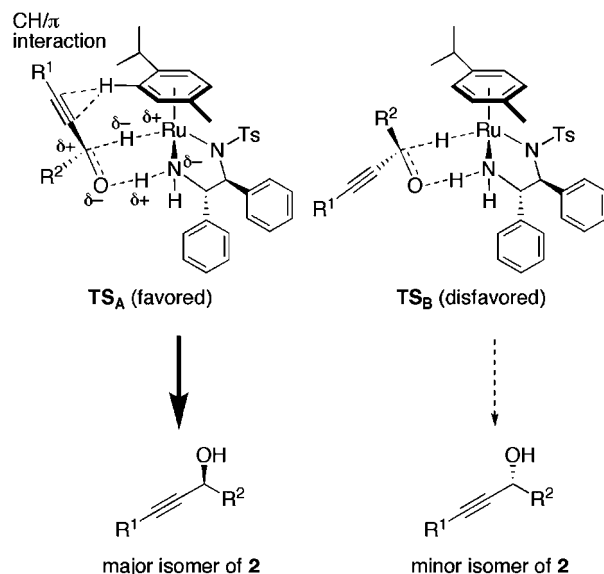


Figure 2. Diastereomeric transition state models (TSs) in the hydrogenation of **1** with (*S,S*)-**3**.

(see the Supporting Information). Figure 2 illustrates the diastereomeric transition state models, **TS_A** and **TS_B**, for hydrogenation of the alkynyl ketone **1** with the RuH[(*S,S*)-TsDPEN] species. The H^{δ-}–Ru^{δ+}–N^{δ-}–H^{δ+} quadrupole of the Ru species and the C^{δ+}=O^{δ-} dipole form six-membered pericyclic structures.^{7,12,13} Ketone is hydrogenated in the outer coordination sphere of the active species, where neither carbonyl/Ru nor alkyne/Ru interaction is involved. This characteristic TS structure results in the high chemoselectivity of carbonyl groups over the alkyne moieties.¹⁴ The **TS_A** is expected to be stabilized by the attractive CH/π interaction between the *p*-cymene (arene) CH and the alkyne π-system as previously proposed for the reaction of the aromatic ketone.^{12,13} Thus, the major enantiomer of propargylic alcohol **2** is produced through the **TS_A**. The consistently high enantioselectivity through the reactions of alkynyl ketones **1a–1d** with alkyl groups of various sizes as R² (Table 1, entries 1 and 4–6) supports these TS models. The low enantioselectivity in the reaction of the alkynyl phenyl ketone **1e**, which has π-systems on both sides of the carbonyl moiety, can be explained by using these models (Table 1, entry 7). The observation that the electron-rich 4'-CH₃O-substituted phenyl ethynyl ketone **1l** was hydrogenated with higher enantioselectivity than that of the reaction of the electron-deficient 4'-Cl-substituted substrate **1k** is also reasonable according to the CH/π interaction-directed enantioselection (Table 1, entries 13 and 14).

In summary, we have described the first example of the highly enantioselective hydrogenation of alkynyl ketones catalyzed by the η^6 -arene/TsDPEN–Ru(II) triflate **3**. The reaction is conducted with an S/C as high as 5000 to

(14) (a) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417–10418. (b) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73.

afford the propargylic alcohols in up to 97% ee. The C—C triple bonds are left intact in most cases, although these functionalities in the alkynyl ketones (substrates) and the propargylic alcohols (products) are extremely reactive to the hydrogenation with the conventional catalysts. A series of alkyl alkynyl ketones including α -chloro ketone and the substrate with an ene-yne moiety are converted to the desired propargylic alcohols in high yield. The mode of enantioselection is elucidated with the transition state models directed by the CH/ π attractive interaction.

Acknowledgment. This work was supported by Grants-in-Aid from the Japan Science and Technology Agency

(No. AS242Z01398Q), the Japan Society for the Promotion of Science (JSPS) (No. 24350042), and the MEXT (Japan) program “Strategic Molecular and Materials Chemistry through Innovative Coupling Reactions” of Hokkaido University.

Supporting Information Available. Preparative methods and properties of chiral Ru complex **3**, procedures for asymmetric hydrogenation of alkynyl ketones, NMR, GC, and HPLC behavior of products, together with $[\alpha]_D$ values and absolute-configuration determinations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.