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Asymmetric Direct Alkynylation Catalyzed by Chiral Ru−Bis(oxazolinyl)phenyl Complexes

Jun-ichi Ito, Ryosuke Asai, and Hisao Nishiyama*

Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Chikusa Nagoya, Japan

hnishi@apchem.nagoya-u.ac.jp

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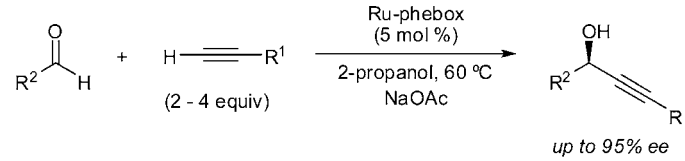
ABSTRACT



Propargylic alcohols were obtained with excellent enantioselectivities in the asymmetric direct alkynylation of aldehydes using 5 mol % of chiral ruthenium complexes containing the chiral bis(oxazolinyl)phenyl ligand.

Transition-metal complexes containing anionic meridional ligands, namely, PCP and NCN pincer ligands, are of interest in homogeneous catalysts for transformation of organic molecules.[1] In recent years, several optically active pincer complexes with chiral meridional ligands have been investigated as asymmetric catalysts.[2] Among these chiral pincer complexes, our and other groups have reported the chiral bis(oxazolinyl)phenyl (phebox) ligands for constructing transition-metal NCN complexes.[3] In this context, we demonstrated that the Rh−phebox complexes have multiple potentials in catalytic asymmetric reactions: allylation, hetero-Diels−Alder, Michael addition, hydrosilylation, conjugate reduction, reductive aldol reaction, direct aldol reaction, and β-boration with high enantiomeric induction.[4,5] As an extension of our research on the phebox complex, we recently reported the Ru analogue, which was successfully utilized in catalytic asymmetric hydrogenation, transfer hydrogenation, and cyclopropanation with excellent enantioselectivity.[6] These results promoted us to investigate further application of the Ru−phebox complexes.

Asymmetric alkynylation with terminal alkynes can provide optically active propargylic alcohols that are useful for materials science or pharmaceutical chemistry.[7−10] Recently, catalytic direct asymmetric alkynylation with chiral Zn,[11]

(1) (a) Albrecht, M.; van Koten, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 3750. (b) van der Boom, M. E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759. (c) *The Chemistry of Pincer Compounds*; Morales-Morales, D., Jensen, C. M., Eds.; Elsevier: Oxford, 2007.

(2) For recent examples: (a) Medici, S.; Gagliardo, M.; Williams, S. B.; Chase, P. A.; Gladiali, S.; Lutz, M.; Spek, A. L.; van Klink, G. P. M.; van Koten, G. *Helv. Chem. Acta* **2005**, *88*, 694. (b) Yoon, M. S.; Ramesh, R.; Kim, J.; Ryu, D.; Ahn, K. H. *J. Organomet. Chem.* **2006**, *691*, 5927. (c) Williamsa, B. S.; Dania, P.; Lutzb, M.; Spek, A. L.; van Koten, G. *Helv. Chem. Acta* **2001**, *84*, 3519. (d) Albrecht, M.; Kocks, B. M.; Spek, A. L.; van Koten, G. *J. Organomet. Chem.* **2001**, *624*, 271. (e) Gosiewska, S.; Huis in't Veld, M.; de Pater, J. J. M.; Bruijnincx, P. C. A.; Lutz, M.; Spek, A. L.; van Koten, G.; Gebbinka, R. J. M. K. *Tetrahedron: Asymmetry* **2006**, *17*, 674. (f) Longmire, J. M.; Zhang, X. *Organometallics* **1998**, *17*, 4374. (g) Gorla, F.; Togni, A.; Venanzi, L. M. *Organometallics* **1994**, *13*, 1607. (h) Baber, R. A.; Bedford, R. B.; Betham, M.; Blake, M. E.; Coles, S. J.; Haddow, M. F.; Hursthouse, M. B.; Orpen, A. G.; Pilarski, L. T.; Pringle, P. G.; Wingad, R. L. *Chem. Commun.* **2006**, 3880. (i) Wallner, O. A.; Olsson, V. J.; Eriksson, L.; Szabó, K. J. *Inorg. Chim. Acta* **2006**, *359*, 1767. (j) Aydin, J.; Kumar, K. S.; Sayah, M. J.; Wallner, O. A.; Szabó, K. J. *J. Org. Chem.* **2007**, *72*, 4689. (k) Takenaka, K.; Minakawa, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2005**, *127*, 12273.

(3) (a) Motoyama, Y.; Makihara, N.; Mikami, Y.; Aoki, K.; Nishiyama, H. *Chem. Lett.* **1997**, 951. (b) Denmark, S. E.; Stavenger, R. A.; Faucher, A.-M.; Edwards, J. P. *J. Org. Chem.* **1997**, *62*, 3375. (c) Stark, M. A.; Richards, C. J. *Tetrahedron Lett.* **1997**, *38*, 5881.

(4) (a) Nishiyama, H. *Chem. Soc. Rev.* **2007**, *36*, 1133. (b) Nishiyama, H.; Ito, J. *Chem. Commun.* **2010**, *46*, 203. (c) Nishiyama, H.; Ito, J. *Chem. Rec.* **2007**, *7*, 159.

(5) Shiomi, T.; Adachi, T.; Toribatake, K.; Zhou, L.; Nishiyama, H. *Chem. Commun.* **2009**, 5987.

(6) (a) Ito, J.; Ujiie, S.; Nishiyama, H. *Chem. Commun.* **2008**, 1923. (b) Ito, J.; Ujiie, S.; Nishiyama, H. *Organometallics* **2009**, *28*, 630. (c) Ito, J.; Ujiie, S.; Nishiyama, H. *Chem.−Eur. J.* **2010**, *16*, 4986.

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In,[12] and Cu[13] catalysts was developed by Carreira et al., Shibasaki et al., and Sawamura et al., respectively. Here we report a new ruthenium-catalyzed alkynylation reaction by use of chiral Ru−phebox complexes (Figure 1).

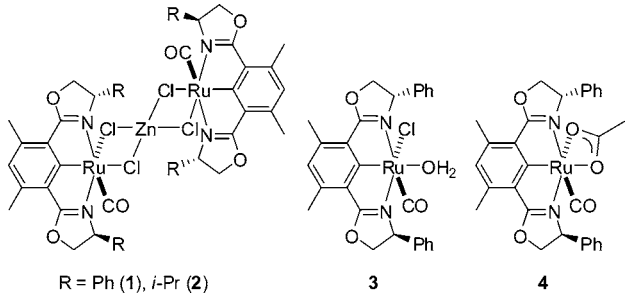
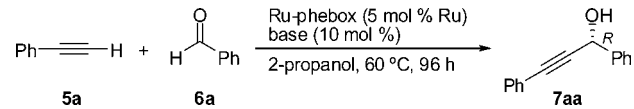


Figure 1. Chiral Ru−bis(oxazolinyl)phenyl complexes.

The addition of phenylacetylene **5a** to benzaldehyde **6a** was investigated using the Ru−phebox complex **1**[6b] as a catalyst (Table 1). Initially, the addition reaction under heating at 60 °C for 96 h in 2-propanol did not proceed (entry 1). However, addition of NaOAc (10 mol %) promoted the reaction to give the corresponding propargylic alcohol **7aa** in 75% yield and 92% ee (entry 2). The substituents on the ligand affected the outcome of the addition reaction. Thus, the use of isopropyl catalyst **2** decreased both the yield and the enantioselectivity (entry 3). Next, we utilized mononuclear complexes **3** and **4** as catalysts. The aqua complex **3** and the acetate complex **4** with NaOAc afforded the propargylic alcohol **7aa** with excellent enantioselectivity of up to 93% ee (entries 4 and 5). Notably, **4** did not require extra NaOAc to give **7aa** in a similar yield and enantioselectivity (entry 6). Other carboxylate reagents were also effective for the addition reaction to produce **7aa** with up to 94% ee (entries 7−11). In contrast to the carboxylate derivatives, other bases, such as NaOMe and K_2CO_3, decreased the enantioselectivity. The use of an excess amount (4 equiv) of the alkyne increased the yield of **7aa** to 89% for 96 h and 83% for 48 h (entries 12 and 13).[14] We also verified that the enantioselectivity of **7aa** was not changed during the catalytic reaction (Figure S1 in Supporting Information).

Table 1. Asymmetric Alkynylation of Benzaldehyde **6a** with Phenylacetylene **5a** Catalyzed by Ru−Bis(oxazolinyl)phenyl Complexes **1**−**4**[a]



entry	cat.	base	yield[b] (%)	ee[c] (%)
1	**1**	−	0	−
2	**1**	NaOAc	75	92
3	**2**	NaOAc	57	60
4	**3**	NaOAc	74	93
5	**4**	NaOAc	74	92
6	**4**	−	71	92
7	**1**	$PhCO_2Na$	69	94
8	**1**	LiOAc	73	92
9	**1**	KOAc	73	90
10	**1**	NaOMe	72	82
11	**1**	K_2CO_3	70	72
12[d]	**1**	NaOAc	89	93
13[e]	**1**	NaOAc	83	93

[a] Reaction conditions: **5a** (2 mmol), **6a** (1 mmol), Ru−phebox (5 mol % Ru), base (0.1 mmol), 2-propanol (5 mL), 60 °C, 96 h. [b] Isolated yield. [c] Determined by HPLC. [d] **5a** (4 mmol). [e] **5a** (4 mmol), 60 °C, 48 h.

The use of THF showed yields similar to that of 2-propanol, but the enantioselectivity was slightly decreased (Table 2, entry 1). In this case, the formation of unidentified byproducts was observed. The reaction in 1,2-dichloroethane was not efficient (entry 2). Use of toluene afforded **7aa** in good enantioselectivity but moderate yield (entry 3). To elucidate the solvent effect, the reaction was monitored by ^{1}H NMR spectroscopy in both toluene-d_8 and 2-propanol-d_8. In toluene-d_8, decay of **7aa** was observed after reaching

(7) (a) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963. (b) Pu, L. *Tetrahedron* **2003**, *59*, 9873. (c) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095. (d) Lu, G.; Li, Y.-M.; Li, X.-S.; Chan, A. S. C. *Coord. Chem. Rev.* **2005**, *249*, 1736. (e) Tyrrell, E. *Curr. Org. Chem.* **2009**, *13*, 1540.

(8) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 937.

(9) Selected examples; (a) Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151. (b) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (c) Li, X.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636. (d) Gao, G.; Xie, R.-G.; Pu, L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5417. (e) Trost, B. M.; Weiss, A. H.; von Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8. (f) Wolf, C.; Liu, S. *J. Am. Chem. Soc.* **2006**, *128*, 10996. (g) Gao, G.; Wang, Q.; Yu, X.-Q.; Xie, R.-G.; Pu, L. *Angew. Chem., Int. Ed.* **2006**, *118*, 128. (h) Trost, B. M.; Chan, V. S.; Yamamoto, D. *J. Am. Chem. Soc.* **2010**, *132*, 5186.

(10) Examples of achiral catalysts; (a) Tzalis, D.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1463. (b) Babler, J. H.; Liptak, V. P.; Phan, N. *J. Org. Chem.* **1996**, *61*, 416. (c) Miyamoto, H.; Yasaka, S.; Tanaka, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 185. (d) Ishikawa, T.; Mizuta, T.; Hagiwara, K.; Aikawa, T.; Kudo, T.; Saito, S. *J. Org. Chem.* **2003**, *68*, 3702. (e) Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363. (f) Sakai, N.; Kanada, R.; Hirasawa, M.; Konakahara, T. *Tetrahedron* **2005**, *61*, 9298. (g) Yao, X.; Li, C.-J. *Org. Lett.* **2005**, *7*, 4395. (h) Dhondi, P. K.; Chisholm, J. D. *Org. Lett.* **2006**, *8*, 67. (i) Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* **2002**, *43*, 8323.

(11) (a) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (b) Jiang, B.; Chen, Z; Xiong, W. *Chem. Commun.* **2002**, 1524. (c) Chen, Z.; Xiong, W.; Jiang, B. *Chem. Commun.* **2002**, 2098. (d) Yamashita, M.; Yamada, K.-i.; Tomioka, K. *Adv. Synth. Catal* **2005**, *347*, 1649. (e) Emmerson, D. P. G.; Hems, W. P.; Davis, B. G. *Org. Lett.* **2006**, *8*, 207.

(12) (a) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760. (b) Harada, S.; Takita, R.; Ohshima, T.; Matsunaga, S.; Shibasaki, M. *Chem. Commun.* **2007**, 948.

(13) (a) Asano, Y.; Hara, K.; Ito, H.; Sawamura, M. *Org. Lett.* **2007**, *9*, 3901. (b) Asano, Y.; Ito, H.; Hara, K.; Sawamura, M. *Organometallics* **2008**, *27*, 5984.

(14) Typical procedure for **7aa** (Table 1, entry 13): To a mixture of **1** (31 mg, 0.025 mmol Ru) and NaOAc (8.2 mg, 0.10 mmol) in *i*PrOH (5 mL), **5a** (408 mg, 4.0 mmol) and **6a** (106 mg, 1.0 mmol) were added at room temperature, and the mixture was stirred at 60 °C for 48 h. Then, the reaction mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography with hexane/ethyl acetate (10:1) as eluent to give **7aa** (173 mg, 0.83 mmol) in 83% yield and 93% ee as determined by HPLC analysis. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (d, J = 5.9 Hz, 1H, OH), 5.71 (d, J = 5.9 Hz, 1H, CH), 7.28−7.51 (m, 8H, CH), 7.68−7.64 (m, 2H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 65.0, 86.5, 88.6, 122.2, 126.5, 128.0, 128.2, 128.3, 128.4, 131.5, 140.3. IR (KBr): ν 3363, 3061, 3031, 2228 cm^{-1}. HRMS: *m*/*z* 208.0902 [M^+], 208.0888 [$C_{15}H_{12}O$]; chiral HPLC (Daicel CHIRALCEL OD, hexane: *i*PrOH = 80:20, 254 nm): tr = 8.2 (major), 12.1 (minor) min, 93% ee; $[\alpha]_D^{20}$ = +7.5 (c = 1.0 in EtOH) {lit.[9a] $[\alpha]_D^{23}$ = +7.0 [c = 1.0 in EtOH, 96% ee (R)]}.

Table 2. Alkynylation of **6a** with **5a** Catalyzed by **1** in Various Solvents[a]

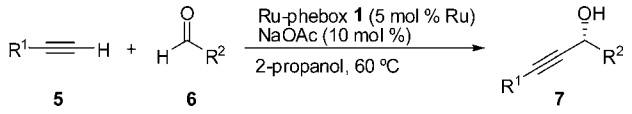
entry	solvent	yield[b] (%)	ee[c] (%)
1	THF	72	87
2	1,2-dichloroethane	48	78
3	toluene	51	90
4	methanol	60	95
5	ethanol	64	94

[a] Reaction conditions: **5a** (2 mmol), **6a** (1 mmol), **1** (5 mol % Ru), NaOAc (0.1 mmol), solvents (5 mL), 60 °C, 96 h. [b] Isolated yield. [c] Determined by HPLC.

its maximum value probably due to a consecutive reaction (Figure S2 in Supporting Information). In contrast, such a phenomenon was not observed in 2-propanol-d_8. Interestingly, other alcohols also provided higher enantioselectivity (up to 95% ee, entries 4 and 5). However, the yields of **7aa** in methanol and ethanol were lower than those in 2-propanol.

Next, the addition reaction of several alkynes to aromatic or aliphatic aldehydes was examined using the Ru−phebox complex **1** (5 mol % Ru) and NaOAc (10 mol %) in 2-propanol at 60 °C (Table 3). Benzaldehyde derivatives with electron-withdrawing groups at the para-position gave better

Table 3. Asymmetric Alkynylation of Aldehydes **6** with Alkynes **5** Catalyzed by **1**[a]



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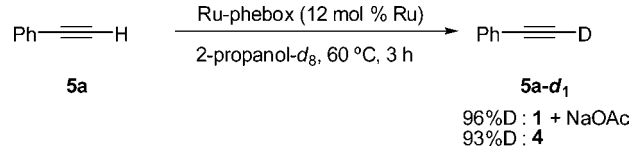
entry	product R[1]; R[2]	time (h)	yield[b] (%)	ee[c] (%)
1	Ph; 4-$CF_3C_6H_4$ (**7ab**)	48	94	90
2	Ph; 4-BrC_6H_4 (**7ac**)	48	93	93
3	Ph; 4-$NO_2C_6H_4$ (**7ad**)	24	88	89
4	Ph; 4-MeC_6H_4 (**7ae**)	96	70	95
5	Ph; 4-$MeOC_6H_4$ (**7af**)	96	42	95
6	Ph; 3-BrC_6H_4 (**7ag**)	48	95	94
7	Ph; 2-BrC_6H_4 (**7ah**)	48	95	77
8	Ph; 1-naphthyl (**7ai**)	48	86	94
9	Ph; 2-naphthyl (**7aj**)	48	82	95
10	Ph; C_6H_{11} (**7ak**)	96	98	73
11	4-MeC_6H_4; Ph (**7ba**)	96	93	93
12	4-$CF_3C_6H_4$; Ph (**7ca**)	96	53	94
13	C_6H_{11}; Ph (**7da**)	96	24	89
14	$SiMe_3$; Ph (**7ea**)	96	21	95

[a] Reaction conditions: **5** (4 mmol), **6** (1 mmol), **1** (0.025 mmol), NaOAc (0.1 mmol), 2-propanol (5 mL), 60 °C. [b] Isolated yield. [c] Determined by HPLC.

yields than those with electron-donating groups (entries 1−5). In each case, the enantioselectivity of the propargylic alcohols **7ab**−**7af** showed excellent values (up to 95% ee). Other aromatic aldehydes, 3-bromobenzaldehyde and 1- and 2-naphthaldehydes, exhibited high yields and excellent enantioselectivity (entries 6, 8, and 9). Although the reaction of **5a** with cyclohexanecarboxaldehyde as a aliphatic aldehyde also gave the corresponding propargylic alcohol **7ak** in a high yield, the decrese in the ee value was observed (entry 10). Addition of other alkynes **5b**−**5e** to benzaldehyde **6a** proceeded with high enantioselectivity (entries 11−14). However, use of **5c**−**e** resulted in low yields of the corresponding alcohols (entries 12−14). It is noteworthy that the Ru−phebox complex **1** could be recovered as the acetate complex **4** in 49% yield after separation by silica gel column chromatography (entry 7).

To gain further insight into the catalytic reaction, the reaction of **5a** with Ru−phebox complexes in 2-propanol-d_8 was monitored by ^{1}H NMR spectroscopy at 60 °C (Scheme 1). Interestingly, it was found that **1** and **4** catalyzed

Scheme 1. H/D Exchange of **5a** with 2-Propanol-d_8 Catalyzed by Ru−phebox Complexes



the H/D exchange reaction between the C(sp)-H of **5a** and 2-propanol-d_8 to give **5a**-d_1 (96% D for **1**, 93% D for **4**). In those reactions, an expected ruthenium acetylide complex was not detected.

In summary, we have developed a highly enantioselective direct alkynylation reaction of aldehydes mediated by novel chiral ruthenium complexes bearing phebox ligands. Further investigation on the scope and limitations of the substrates and the reaction mechanism are underway in our laboratory.

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

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