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Cobalt-catalyzed asymmetric addition of silvlacetylenes to oxa- and azabenzonorbornadienes†

Takahiro Sawano, Keiyu Ou, Takahiro Nishimura* and Tamio Hayashi*

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Asymmetric addition of silylacetylenes to meso-oxa- and azabenzonorbornadienes took place in the presence of a cobalt/ **OuinoxP*** catalyst to give the addition products in good yields with high enantioselectivity.

Transition metal-catalyzed desymmetrization of meso-bicyclic alkenes is a fundamentally important reaction for the synthesis of chiral building blocks.¹ Palladium- and rhodium-catalyzed asymmetric transformations of oxa- and azabicyclic alkenes have been extensively studied, where enantioposition-selective addition of oxygen, nitrogen, and carbon nucleophiles brings about desymmetrization of their meso structures and subsequent ring-opening reactions provide access to enantioenriched compounds bearing multiple stereocenters in a single step.²⁻⁵ Of several carbon nucleophiles, organozinc and -boron reagents have been often used in the asymmetric addition to meso-bicyclic alkenes, while the asymmetric addition of terminal alkynes remains to be developed. In 2002, Cheng and co-workers reported the first nickel-catalyzed ring-opening alkynylation of oxa- and azabicyclic alkenes, where racemic 2-alkynyl-1,2-dihydronaphthalene derivatives were produced in high yields with high diastereoselectivity.6 Rhodium-catalyzed asymmetric alkynylations of azabenzonorbornadienes⁷ and bicyclic hydrazines⁸ involving the ring-opening were also reported. On the other hand, Tenaglia et al. reported hydroalkynylation of oxabenzonorbornadienes without the ring-opening, which is catalyzed by a phosphapalladacycle complex giving racemic 2-alkynyl-1,2,3,4-tetrahydro-1,4-epoxynaphthalenes.^{9,10} Here we report the first example of catalytic asymmetric addition of terminal alkynes to oxabenzonorbornadienes without the ring-opening, which was achieved by use of a chiral phosphine-cobalt catalyst system.

We recently reported cobalt-catalyzed addition of silylacetylenes to α , β -unsaturated ketones giving β -alkynyl ketones.¹¹ As a part of our continuing efforts in developing cobalt-catalyzed reactions, we examined the catalytic activity of cobalt(1)

Kyoto University, Sakyo, Kyoto 606-8502, Japan.

E-mail: tnishi@kuchem.kyoto-u.ac.jp, thayashi@kuchem.kyoto-u.ac.jp; Fax: +81 75 753 3988; Tel: +81 75 753 3987

complexes in the addition of silylacetylenes to oxabenzonorbornadienes, and we found that the alkynylation proceeds

without the ring-opening to give hydroalkynylation products. Thus, treatment of oxabenzonorbornadiene 1a with 2 equiv. of (triisopropylsilyl)acetylene (2m) in the presence of $Co(OAc)_2$. 4H₂O (5 mol%), 1,2-bis(diphenylphosphino)ethane (dppe) (5 mol%), and zinc powder (50 mol%) in dimethyl sulfoxide (DMSO) at 80 °C for 20 h, which are standard conditions for the cobalt-catalyzed alkynylation of enones, gave 1,2,3,4tetrahydro-2-alkynyl-1,4-epoxynaphthalene 3am in 73% yield (Table 1, entry 1). For the development of an asymmetric variant of this reaction, several chiral bisphosphine ligands were tested (entries 2–7). A cobalt/(S,S)-chiraphos catalyst efficiently catalyzed the present reaction to give 3am in 84% yield, but the ee was moderate (54% ee, entry 2). The use of (S,S)-bdpp, which enables the cobalt-catalyzed asymmetric alkynylation of conjugated enones with high enantioselectivity,11 gave a low yield of 3am (17% yield, entry 3). Some other chiral bisphosphine ligands were examined (entries 4–7), and (R,R)-QuinoxP*^{2d} was found to show the highest enantioselectivity (67% ee, entry 7).¹² The reaction temperature significantly affected both the yield and the enantioselectivity (entries 8 and 9). Thus, the reaction by use of (R,R)-QuinoxP* at 10 °C proceeded to give 3am in 90% yield with 99% ee (entry 9). The yield and enantioselectivity of **3am** were kept high (91%, 99% ee) in the reaction with a reduced amount (10 mol%) of zinc powder (entry 10). The reaction in the absence of zinc gave only 21% yield of **3am** (entry 11), implying that an active catalytic species is formed by reduction of cobalt(II) acetate with zinc.11

Table 2 summarizes the results obtained from the reaction of several oxabenzonorbornadienes 1 with silvlacetylenes 2, which was carried out in the presence of cobalt/(R,R)-QuinoxP* as a catalyst (5 mol%). The reaction of meso-oxabenzonorbornadienes 1a-1f bearing substituents (Me, F, Br, and OMe) on the benzene ring gave the corresponding addition products 3am-3fm in high yields with high enantioselectivity (90-99% ee) (entries 1-6). The present cobalt-catalyzed alkynylation can introduce bulky silylacetylene 2n with high enantioselectivity (entries 7 and 8), but the addition of less bulky (triethylsilyl)acetylene (20) to 1a gave only 7% of the addition product 3ao (entry 9) and phenylacetylene (2p) and 1-octyne (2q) were not applicable (entries 10 and 11). Azabenzonorbornadienes 1g and 1h were also good substrates in the addition of 2m to give 3gm and 3hm

Department of Chemistry, Graduate School of Science,

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Table 1 Cobalt-catalyzed asymmetric alkynylation of oxabenzo-
norbornadiene $\mathbf{1a}^a$



^a Reaction conditions: 1a (0.20 mmol), (triisopropylsilyl)acetylene
(2m) (0.40 mmol), Co(OAc)₂·4H₂O (5 mol%), ligand (5 mol%), Zn (50 mol%), DMSO (0.3 mL) for 20 h. ^b Conversion of 1a determined by ¹H NMR. ^c Isolated yield. ^d Determined by chiral HPLC analysis. ^e Not determined. ^f Zn (10 mol%) was used. ^g Performed without Zn.

in 73% and 70% yield with 96% and 95% ee, respectively (entries 12 and 13).



The same type of addition was observed in the reaction of oxanorbornadiene **4** with alkyne **2m** to give hydroalkynylation product **5** in 60% yield with 95% ee (eqn (1)).¹³

The relative and absolute configuration of 3em was determined to be 1S,2R,4R by X-ray analysis of 6, which was

 Table 2
 Asymmetric alkynylation of oxa- and azabenzonorbornadiene^a

R ¹ R ¹	$ \begin{array}{c} $	33	Co(OAc) ₂ ·4I (5 mol%) (<i>R</i> , <i>R</i>)-Quino (5 mol%) Zn (10 mol% DMSO, 10 °	$\begin{array}{c} H_2O \\ xP^* \\ \hline 6) \\ C, 20 h \\ \end{array} \begin{array}{c} R^1 \\ R^1 \\ F \\ \end{array}$	2 ² X 2 ² 3	R ³
Entry	Х	\mathbf{R}^1	R ²	R ³	$\operatorname{Yield}^{b}(\%)$	ee^{c} (%)
1	0	Н	H (1a)	Si(<i>i</i> -Pr) ₃ (2m)	91 (3am)	99
2^d	0	Me	H (1b)	Si(<i>i</i> -Pr) ₃ (2m)	82 (3bm)	99
$3^{d,e}$	0	F	H (1c)	Si(<i>i</i> -Pr) ₃ (2m)	86 (3cm)	90
$4^{d,e}$	0	Br	H (1d)	$Si(i-Pr)_3$ (2m)	81 (3dm)	94
$5^{d,e}$	0	Br	Me (1e)	Si(<i>i</i> -Pr) ₃ (2m)	70 (3em)	95
6	0	Н	OMe (1f)	$Si(i-Pr)_3$ (2m)	91 (3fm)	97
$7^{d,f}$	0	Br	Me (1e)	$SiPh_2(t-Bu)$ (2n)	60 (3en)	90 ^g
8	0	Н	OMe (1f)	$SiPh_2(t-Bu)$ (2n)	90 (3fn)	96
9	0	Н	H (1a)	SiEt ₃ (20)	7 (3ao)	80
10	0	Н	H (1a)	Ph (2p)	0 (3ap)	
11	0	Н	H (1a)	C_6H_{13} (2q)	0 (3aq)	
12^{d}	NBoc	Н	H (1g)	$Si(i-Pr)_3$ (2m)	73 (3gm)	96 ^g
$13^{d,f}$	NBoc	Me	H (1h)	Si(<i>i</i> -Pr) ₃ (2m)	70 (3hm)	95 ^g

^{*a*} Reaction conditions: **1** (0.20 mmol), alkyne **2** (0.40 mmol), Co(OAc)₂·4H₂O (5 mol%), (*R*,*R*)-QuinoxP* (5 mol%), Zn (10 mol%), DMSO (0.30 mL) at 10 °C for 20 h. ^{*b*} Isolated yield of **3**. ^{*c*} Determined by chiral HPLC analysis. ^{*d*} For 48 h. ^{*e*} Reaction at 15 °C. ^{*f*} Reaction at 30 °C. ^{*g*} ee values were determined by chiral HPLC analysis of desilylated products of **3**.



Fig. 1 ORTEP illustration of compound 6 with thermal ellipsoids drawn at the 50% probability level.

obtained by treatment of **3em** with tetrabutylammonium fluoride (eqn (2), Fig. 1).¹⁴

To gain information about the catalytic cycle, we carried out deuterium labeling experiments starting with deuterated silylacetylenes. The reaction of oxabenzonorbornadiene **1f** with the deuterated alkyne **2m**-*d* under the standard reaction conditions gave **3fm**-*d*, which showed 97% of deuterium-incorporation at the 3-*exo*-position (eqn (3)).¹⁵ On the other hand, treatment of **1f** with an equimolar mixture of the deuterated alkyne **2m**-*d* and (*tert*-butyldiphenysilyl)acetylene (**2n**) gave addition





Scheme 1 Proposed catalytic cycle.

products **3fm** and **3fn** in 39% and 54% yield, respectively, where both products partially contained deuterium (H/D = 1.3 for **3fm** and H/D = 1.4 for **3fn**) (eqn (4)).¹⁶ These results indicate that hydroalkynylation proceeds *via syn*-addition of the terminal alkyne and the terminal proton is the hydrogen source of the addition product. In addition, the observed scrambling between hydrogen and deuterium implies that the present alkynylation includes carbometalation and protonation steps (*vide infra*).



Scheme 1 illustrates the catalytic cycle proposed for the present cobalt-catalyzed alkynylation. It is likely that the catalytic reaction is initiated by the reduction of cobalt(I) to cobalt(1) by zinc powder giving a cobalt(1) acetate \mathbf{A} ,¹⁷ which undergoes the reaction with a terminal alkyne to form an alkynylcobalt(1) \mathbf{B} and acetic acid.¹⁸ An approach of the alkynylcobalt \mathbf{B} from the *exo* direction of oxabenzonorbornadiene followed by *syn*-carbometalation to form an alkylcobalt(1) species \mathbf{C} . Protonation of alkylcobalt \mathbf{C} with the terminal alkyne gives the alkynylation product and regenerates the alkynylcobalt intermediate \mathbf{B} .

In summary, we have developed a cobalt-catalyzed addition of silylacetylenes to oxa- and azabenzonorbornadienes giving the corresponding addition products with high enantioselectivity.

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