Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201701593

Link to VoR: http://dx.doi.org/10.1002/adsc.201701593

10.1002/adsc.201701593

UPDATE

DOI: 10.1002/adsc.201

Enantioselective Cyanosilylation of Alkynyl Ketones Catalyzed by Combined Systems Consisting of Chiral Ruthenium(II) Complex and Lithium Phenoxide

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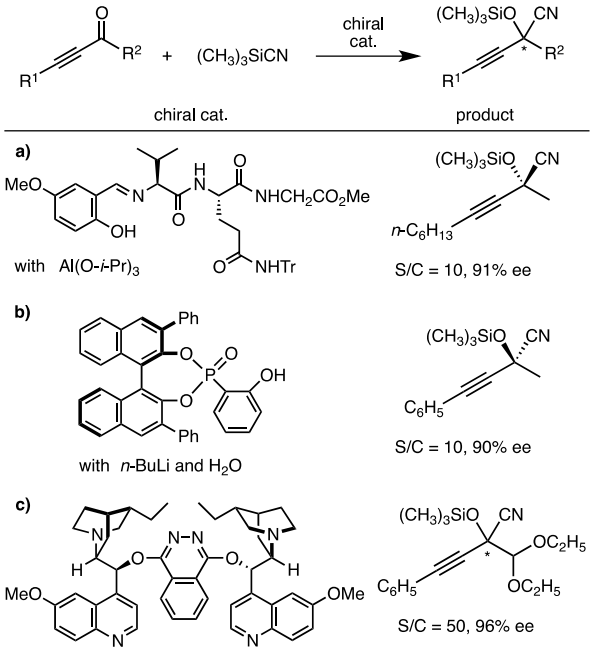
Received:

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

Abstract. Asymmetric cyanosilylation of alkynyl ketones with the catalyst systems consisting of amino acid/2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) /ruthenium(II) complex and lithium phenoxide (Ru•Li cat.) was studied. The reaction was conducted in *tert*-butyl methyl ether (TBME) at –78 °C with a substrate-to-catalyst molar ratio (S/C) as high as 2000. A series of simple and functionalized ketones was converted into the alkynyl tertiary cyanohydrin derivatives in up to 99% ee. Appropriate selection of an amino-acid ligand of the catalyst according to the substrate structure was crucially important to achieve high enantioselectivity and a wide scope of substrates. Transformation of the chiral cyanohydrin product into a functionalized lactone was also examined.

Keywords: alkynyl ketones; asymmetric catalysis; bimetallic catalysts; cyanosilylation; lithium; ruthenium

Development of catalytic asymmetric reactions to produce chiral tertiary alcohol derivatives is among the central targets in the research area of synthetic organic chemistry. Enantioselective cyanosilylation of ketones is the representative method for this purpose.[1] The chiral tertiary cyanohydrin products are regarded as a class of functionalized tertiary alcohol derivatives. Many chiral organometallic catalysts and organocatalysts have been developed for this important transformation.[1] However, only three substrates were examined for the reaction of alkynyl ketones as follows (Scheme 1).[2] a) A chiral peptide ligand–Al(O-*i*-Pr)$_3$ system catalyzed the reaction of 3-decyne-2-one and (CH$_3$)$_3$SiCN with a substrate-to-catalyst molar ratio (S/C) of 10 (–78 °C, 24 h) to give the cyanated product in 66% yield and 91% enantiomeric excess (ee).[2a] b) The reaction of 4-phenyl-3-butyne-2-one catalyzed by a chiral lithium phosphoryl phenoxide with an S/C of 10 (–78 °C, 7 h) gave the product in 95% yield and 90%



Scheme 1. Previous Studies on the Asymmetric Cyanosilylation of Alkynyl Ketones.

ee.[2c] c) An alkynyl α,α-dialkoxymethyl ketone was cyanated with a chiral cinchona alkaloid base at an S/C of 50 (–50 °C, 19 h) to afford the cyanohydrin derivatives in 93% yield and 96% ee.[2b] The catalytic activity and enantioselectivity as well as the substrate scope have room for improvement.

In recent years, a variety of alkyne transformations have been reported, such as the Pauson–Khand reaction, enyne cycloisomerization, chalcogenation, heterocyclization, silaboration, etc.[3] The large number and range of such transformations indicates that the alkyne moiety is a useful carbon-based functional group. Therefore, chiral alkynyl cyanohydrins are expected to be useful multi-functionalized intermediates for the synthesis of

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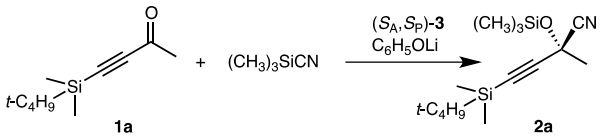
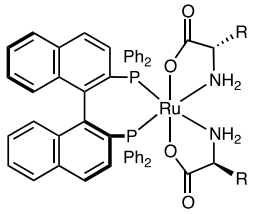
Table 1. Asymmetric Cyanosilylation of Alkynyl Ketone **1a** with Ru Complex **3** and C_6H_5OLi.[a]





(S_A,S_P)-**3**

a: R = C_6H_5, **b**: R = 4-$CH_3OC_6H_4$, **c**: R = 4-$(CH_3)_2NC_6H_4$, **d**: R = 4-ClC_6H_4, **e**: R = *i*-C_3H_7, **f**: R = *t*-C_4H_9,

Entry	**3**	**1a**/**3**/Li	Yield [%][b]	ee [%][b]
1	**3a**	500:1:1	>99(97)[c]	97
2	**3a**	500:1:0.5	>99	97
3[d]	**3a**	2000:1:1	99	97
4	**3b**	500:1:1	98	95
5	**3c**	500:1:1	81	91
6	**3d**	500:1:1	>99	96
7	**3e**	500:1:1	33	–22[e]
8	**3f**	500:1:1	18	–5[e]

[a] Unless otherwise stated, the reactions were carried out using **1a** (1.0 mmol) and $(CH_3)_3SiCN$ (2.0 mmol) in *t*-$C_4H_9OCH_3$ (6 mL) with (S_A,S_P)-**3** and C_6H_5OLi (40 mM or 20 mM in THF) in a ratio shown in the third column at –78 °C for 24 h. [b] Data for (*R*)-**2a** were determined by GC on a chiral stationary phase. [c] The isolated yield is given in parenthesis. [d] Reaction using 3.0 mmol of **1a**. [e] (*S*)-**2a** was the major isomer.

(complex) biologically important compounds. Moreover, these chiral molecules can be connected to the naturally occurring and artificial molecular architectures by means of the click azide–alkyne cycloadditions.[4]

We previously reported the asymmetric cyanosilylation of aromatic, aliphatic, and α,β-unsaturated ketones[5] as well as aldehydes[6] with our original catalyst systems consisting of amino acid/BINAP/Ru(II) complexes **3** and a Li compound (see the scheme in Table 1).[7] We utilized these catalyst systems for the asymmetric reaction of alkynyl ketones into silylated cyanohydrins, and to our delight we achieved high catalytic activity (leading to low catalyst loading), chemoselectivity, and enantioselectivity as well as a wide scope of substrates by appropriate selection of the amino-acid ligand in complex **3** and the reaction conditions. Both simple and hetero-substituted alkynyl ketones were successfully converted to the desired products.

We selected a silyl-substituted alkynyl ketone **1a** as the standard substrate to optimize the catalyst structure (Table 1). The catalyst performance was evaluated with the three categories of 1) activity, 2) 1,2-selectivity over 1,4-selectivity, and 3) enantioselectivity. When **1a** (1.0 mmol) and $(CH_3)_3SiCN$ (2.0 mmol) were reacted in the presence of Ru[(*S*)-phgly]$_2$[(*S*)-binap][8] ((S_A,S_P)-**3a**: 2.0 μmol; S/C = 500) and C_6H_5OLi (40 mM in THF, 2.0 μmol) in *t*-$C_4H_9OCH_3$ at –78 °C for 24 h, the tertiary-cyanohydrin silyl ether (*R*)-**2a** in 97% ee was obtained quantitatively (entry 1). No 1,4-addition product was observed.[9] The excellent enantioselectivity is notable, because the size difference between the alkynyl moiety and methyl is small. The reaction using 0.5 equivalent of C_6H_5OLi to **3a** gave the same enantioselectivity, suggesting that an active 1:1 **3a**–Li^+ complex was formed in this reaction (entry 2).[10] The high catalytic activity of the **3a**–C_6H_5OLi system achieved complete conversion in the reaction at an S/C of 2000 with maintenance of the high enantioselectivity (entry 3). The Ru complexes with 4-AnGly and (4-ClPh)Gly ligands,[8] **3b** and **3d**, showed similar efficiency (entries 4 and 6). Introduction of a strongly electron-donative $(CH_3)_2N$ group on the phenyl ring of the PhGly ligand, **3c**, somewhat decreased the catalytic activity and enantioselectivity (entry 5). Interestingly, the catalytic behavior was drastically changed by using the alkyl-substituted amino-acid ligands, Val and *t*-Leu,[8] instead of PhGly (entries 7 and 8). The catalytic activity and enantioselectivity were both significantly decreased, and the sense of enantioselection was reversed.

The **3**–C_6H_5OLi system was applied to the asymmetric cyanosilylation of a series of alkynyl ketones **1** (Table 2). The silyl-ethynyl methyl ketones **1a**–**1c** were equally cyanated to afford the 1,2-adducts quantitatively with high enantioselectivity under the standard conditions (entries 1–3). The aryl-ethynyl ketones **1d**–**1g** showed different behaviors. The cyanation of the phenyl-ethynyl ketone **1d** with the **3a**–C_6H_5OLi catalyst gave the product **2d** in 85% ee (entry 4). The enantioselectivity was increased by using the 4-AnGly/BINAP/Ru complex **3b** (entry 5). The ee value of 95% was obtained with a 1:0.5 **3b**–C_6H_5OLi system at an S/C of 500 (entry 6). The comparable result was obtained in the reaction with an S/C of 1000 (entry 7). The 2-tolyl-ethynyl substrate **1e** showed similar reactivity and enantioselectivity (entry 8). The reaction of the electron-rich 4-anisyl-ethynyl ketone **1f** was relatively slow, but the cyanated product **2f** was obtained in 99% yield and 94% ee after 72 h (entry 9). The electron-deficient 4-chlorophenyl-ethynyl ketone **1g** showed slightly lower enantioselectivity (entry 10). An alkenyl-ethynyl ketone **1h** was also converted to the 1,2-adduct **2h** under the regular conditions (entry 11). The 4-AnGly complex **3b** showed better enantioselectivity for this substrate (entry 12). The reaction of *tert*-butyl-ethynyl ketone **1i**, an alkyl-ethynyl substrate, using the **3a**–C_6H_5OLi catalyst with an S/C of 100 took 54 h for completion to yield the product **2i** in 92% ee (entry 13). Notably, the cyanation of unsubstituted ethynyl ketone **1j** quantitatively afforded the 1,2-adduct **2j** (entries 14–16). The highest ee value of 92% was obtained when

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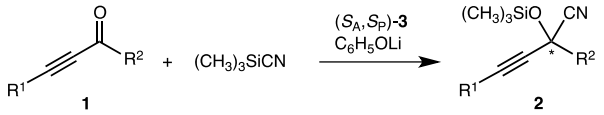
Table 2. Asymmetric Cyanosilylation of Alkynyl Ketones **1**.[a]



a: R¹ = *t*-C₄H₉(CH₃)₂Si, R² = CH₃ **g**: R¹ = 4-ClC₆H₄, R² = CH₃
b: R¹ = *t*-C₄H₉(C₆H₅)₂Si, R² = CH₃ **h**: R¹ = 1-cyclohexenyl, R² = CH₃
c: R¹ = (*i*-C₃H₇)₃Si, R² = CH₃ **i**: R¹ = *t*-C₄H₉, R² = CH₃
d: R¹ = C₆H₅, R² = CH₃ **j**: R¹ = H, R² = CH₃
e: R¹ = 2-CH₃C₆H₄, R² = CH₃ **k**: R¹ = C₆H₅, R² = C₂H₅
f: R¹ = 4-CH₃OC₆H₄, R² = CH₃ **l**: R¹ = C₆H₅, R² = H

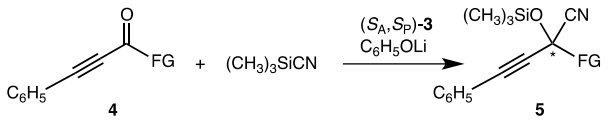
Entry	**1**	**3**	**1**/**3**/Li	Time [h]	Yield [%][b]	ee [%][c]
1	**1a**	**3a**	500:1:1	24	>99(97)	97(*R*)
2	**1b**	**3a**	500:1:1	24	>99(99)	95
3	**1c**	**3a**	500:1:1	24	>99(98)	95
4	**1d**	**3a**	500:1:1	24	>99	85(*R*)
5	**1d**	**3b**	500:1:1	24	>99	94(*R*)
6	**1d**	**3b**	500:1:0.5	24	>99(93)	95(*R*)
7	**1d**	**3b**	1000:1:0.5	24	>99	94(*R*)
8	**1e**	**3b**	500:1:0.5	24	>99(97)	92
9	**1f**	**3b**	500:1:0.5	72	99(90)	94
10	**1g**	**3b**	500:1:0.5	24	99(93)	90
11	**1h**	**3a**	500:1:1	54	95	85
12	**1h**	**3b**	100:1:1	54	99(90)	91
13	**1i**	**3a**	100:1:1	54	>99(88)	92
14	**1j**	**3a**	500:1:1	24	>99[d]	88
15	**1j**	**3b**	500:1:1	24	>99[d]	90
16	**1j**	**3b**	500:1:0.5	24	>99[d]	92
17	**1k**	**3a**	500:1:1	24	>99(98)	55
18	**1l**	**3a**	500:1:1	24	97[e]	90(*R*)

[a] Unless otherwise stated, the reactions were carried out using **1** (1.0 mmol) and $(CH_3)_3SiCN$ (2.0 mmol) in *t*-$C_4H_9OCH_3$ (6 mL) with (S_A,S_P)-**3** and C_6H_5OLi (40 mM or 20 mM in THF) in a ratio shown in the fourth column at –78 °C. [b] Determined by GC or ^1H NMR analysis. The isolated yield is given in parenthesis. [c] Determined by GC or HPLC on a chiral stationary phase. [d] **2j** was a volatile compound. [e] **2l** was partially decomposed on silica gel.

the reaction was catalyzed by the 1:0.5 **3b**–C_6H_5OLi system, although the size difference between ethynyl and methyl is quite small (entry 16). Phenyl-ethynyl ethyl ketone **1k** was a difficult substrate to cyanate with high enantioselectivity, yielding the adduct **2k** in 55% ee (entry 17). The reaction of the alkynyl aldehyde **1l** afforded the secondary-cyanohydrin silyl ether **2l** in 90% ee (entry 18).

We next examined the cyanation of functionalized substrates (Table 3). An alkynyl ketone with an α-methoxy group **4a** was cyanated in the presence of the **3a**–C_6H_5OLi catalyst under the standard conditions to afford the cyanohydrin derivative (*R*)-**5a** in 74% ee quantitatively (entry 1). To our delight, the use of the *t*-Leu/BINAP/Ru(II) complex **3f** instead of **3a** remarkably increased the ee value of **5a** to 95% (entry 2). The structural modifiability is a notable feature of this catalyst. The bidentate-character of **4a** may change the manner of interaction with the catalyst.

Table 3. Asymmetric Cyanosilylation of Functionalized Alkynyl Ketones 4.[a]



a: FG = CH_2OCH_3 **c**: FG = $CH_2CH(OCH_3)_2$
b: FG = $CH(OC_2H_5)_2$ **d**: FG = CO_2CH_3

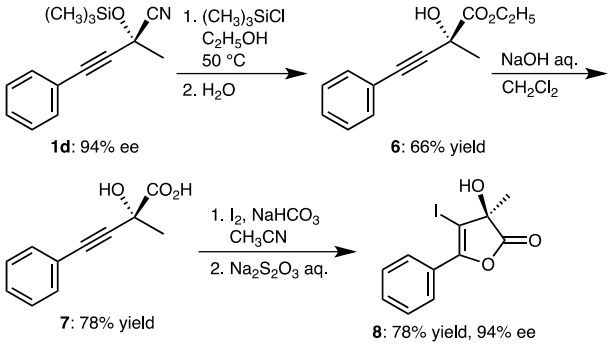
Entry	**4**	**3**	**4**/**3**/Li	Time [h]	Yield [%][b]	ee [%][c]
1	**4a**	**3a**	500:1:1	24	>99	74(*R*)
2	**4a**	**3f**	500:1:1	24	>99	95(*R*)
3	**4a**	**3f**	1000:1:1	24	>99(99)	96(*R*)
4	**4b**	**3a**	500:1:1	24	>99(93)	84
5	**4b**	**3f**	500:1:1	24	>99(94)	99
6	**4c**	**3a**	500:1:1	24	>99(99)	59
7	**4c**	**3f**	500:1:1	24	>99(99)	92
8	**4d**	**3a**	500:1:1	62	75[d]	85
9	**4d**	**3a**	250:1:0.5	62	95[d]	86

[a] Unless otherwise stated, the reactions were carried out using **4** (1.0 mmol) and $(CH_3)_3SiCN$ (2.0 mmol) in *t*-$C_4H_9OCH_3$ (6 mL) with (S_A,S_P)-**3** and C_6H_5OLi (40 mM or 20 mM in THF) in a ratio shown in the fourth column at –78 °C. [b] Determined by GC or ^1H NMR analysis. The isolated yield is given in parenthesis. [c] Determined by GC or HPLC on a chiral stationary phase. [d] A partial reverse reaction to **4d** on silica gel was observed.

The cyanation of **4a** with an S/C of 1000 was completed in 24 h (entry 3). Even higher enantioselectivity of 99% was achieved in the reaction of an α,α-diethoxy alkynyl ketone **4b** with the **3f**–C_6H_5OLi catalyst (entry 5). The **3a**–C_6H_5OLi system showed usable selectivity for this substrate (entry 4). Medium enantioselectivity of 59% was obtained in the cyanation of a β,β-dimethoxy alkynyl ketone **4c** with the **3a**–C_6H_5OLi catalyst (entry 6). A high level of enantioselectivity was again achieved by using the **3f**–C_6H_5OLi catalyst to give **5c** in 92% ee (entry 7). The reaction of an alkynyl α-keto ester **4d** slowly afforded the product **5d** (86% ee) in 95% yield catalyzed by the **3a**–C_6H_5OLi system with an S/C of 250 in 62 h (entries 8 and 9).

The alkynyl cyanohydrin product **1d** was concisely transformed to a 4-iodo-2(3*H*)-furanone derivative with a chiral quaternary carbon **8** without loss of the enantiomeric purity as shown in Scheme 2 (see also the Supporting Information). Thus, **1d** in 94% ee was converted to the α-hydroxy carboxylic acid **7** by using Luo's alcoholysis conditions (**6**: 66% yield) followed by saponification (78% yield).[11] Iodolactonization of **7** reported by Larock afforded **8** in 78% yield and in 94% ee.[12] Further functionalization of **8** would be possible by Pd-catalyzed coupling reactions.[12] The 2(3*H*)-furanone structures containing a chiral center exist in some biologically active molecules.[13,14]

In summary, we have reported highly reactive and enantioselective cyanosilylation of alkynyl ketones catalyzed by the amino acid/BINAP/Ru(II) complex–



Scheme 2. Synthesis of a 4-Iodo-2(3*H*)-furanone Derivative with a Chiral Quaternary Carbon **8**.

C_6H_5OLi systems. The reaction was carried out with an S/C up to 2000, which was about two-orders of magnitude larger than those in previous reports. A series of simple and functionalized substrates was converted into the alkynyl tertiary cyanohydrin silyl ethers in 97% ee for unfunctionalized products and in 99% ee for functionalized compounds by using the catalysts bearing appropriate amino-acid ligands in the best cases. The wide scope of the substrates is notable. To our knowledge the enantioselectivity is the highest yet reported for the cyanosilylation of alkynyl ketones. The cyanohydrin product was readily converted to the 4-iodo-2(3*H*)-furanone derivative without loss of the enantiomeric purity.

Experimental Section

Typical Procedure for the Enantioselective Cyanosilylation of 1a with (S_A,S_P)-3a

To a solution of Ru[(*S*)-phgly]$_2$[(*S*)-binap] ((S_A,S_P)-**3a**) (2.0 mg, 2 μmol), $(CH_3)_3SiCN$ (202 mg, 2.04 mmol) and 4-(*tert*-butyldimethylsilyl)but-3-yn-2-one (**1a**) (179 mg, 0.982 mmol) in *t*-$C_4H_9OCH_3$ (6.0 mL) was added C_6H_5OLi (2 μmol) as a THF solution (40 mM, 50 μL) at –78 ºC under an argon atmosphere. The reaction mixture was continuously stirred for 24 h at the same temperature, then poured into an ice water bath to terminate the reaction. The mixture was extracted 3 times by ethyl acetate (10 mL × 3). The collected organic phase was washed with brine and dried over Na_2SO_4. After the Na_2SO_4 was filtered off, the resulting mixture was concentrated in vacuo. The crude product was purified by silica-gel column chromatography (hexane/ethyl acetate = 4:1) to afford (*R*)-4-(*tert*-butyldimethylsilyl)-2-methyl-2-((trimethylsilyl)oxy)but-3-ynenitrile ((*R*)-**2a**) (269 mg, 97% yield, 97% ee). The ee value of **2a** was determined by chiral GC analysis: chirasil dex (0.32 mm × 25 m), carrier gas: helium (72 kPa), column temp: 110 ºC for 10 min then heating to 190 ºC at a rate of 10 ºC min^{-1}, t_R of (*R*)-**2a**: 8.8 min (98.3 %), t_R of (*S*)-**2a**: 9.3 min (1.7 %), $[\alpha]^{25}_D$ 0.3 (*c* = 1.01, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85 (s, 3H), 0.95 (s, 9H), 0.29 (s, 9H), 0.140 (s, 3H), 0.135 (s, 3H). The procedures and chemical properties of products in detail are described in the Supporting Information.

Acknowledgements

This work was supported by Grants-in-Aid from the Japan Society for the Promotion of Science (JSPS) (No. 15H03802, No. 25410031, and No. 16K17900), the JSPS program "Strategic Young Researcher Overseas Visits Program for Accelerating Brain Circulation" (No. R2401), and the MEXT (Japan) program "Strategic Molecular and Materials Chemistry through Innovative Coupling Reactions" of Hokkaido University.

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10.1002/adsc.201701593

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