

Cobalt-Catalyzed Asymmetric 1,6-Addition of (Triisopropylsilyl)-acetylene to $\alpha,\beta,\gamma,\delta$ -Unsaturated Carbonyl CompoundsTakahiro Sawano,[†] Akram Ashouri,[†] Takahiro Nishimura,^{*,†} and Tamio Hayashi^{*,‡}[†]Department of Chemistry, Graduate School of Science, Kyoto University, Kyoto 606-8502, Japan[‡]Institute of Materials Research and Engineering, A*STAR, 3 Research Link, Singapore 117602

S Supporting Information

ABSTRACT: Asymmetric addition of (triisopropylsilyl)-acetylene to $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds took place in the presence of a cobalt/Duphos catalyst to give the 1,6-addition products in high yields with high regio- and enantioselectivity.

Transition metal-catalyzed asymmetric 1,4-addition of terminal alkynes to β -substituted α,β -unsaturated carbonyl compounds and related compounds is one of the most efficient methods to construct a stereocenter at the propargylic position.¹ An ideal process is the reaction of terminal alkynes in the presence of a truly catalytic amount of a catalyst without using a stoichiometric amount of pre-prepared alkynylmetal reagents in view of the atom efficiency. Since the first report of such an alkynylation by Carreira and co-workers on copper-catalyzed reactions of terminal alkynes with Meldrum's acid derivatives,² several successful examples have been reported by use of Cu,³ Rh,⁴ Co,⁵ and Pd⁶ catalysts.⁷ On the contrary, to the best of our knowledge, the asymmetric addition of terminal alkynes to extended conjugate systems such as $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds has not been achieved to date probably due to the difficulty of controlling the regioselectivity as well as the enantioselectivity.^{8,9} Mitsudo and Watanabe reported ruthenium-catalyzed addition of terminal alkynes to 1,3-dienes, which includes the examples of formal 1,6-addition to dienoates (Scheme 1a).¹⁰ On the other hand, nickel-catalyzed asymmetric addition of terminal

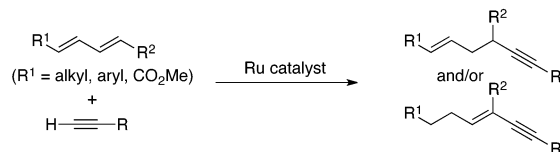
alkynes to 1-aryl-1,3-butadienes was reported by Suginome, where hydroalkynylation proceeds at the terminal alkene to give 1-aryl-3-alkynyl-1-butene with high enantioselectivity (Scheme 1b).¹¹ Here we report the enantioselective 1,6-addition of a terminal alkyne to linear $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds with very high regioselectivity, which is realized by use of a cobalt/chiral bisphosphine catalyst (Scheme 1c).

Recently, we reported that cobalt complexes can catalyze the 1,4-addition of silylacetylenes to conjugated enones, where enoates and enamides were inert under the same reaction conditions.^{5,12} In the course of our ongoing investigation into cobalt-catalyzed alkynylation, we found that the addition of a silylacetylene to conjugated dienoates proceeds with very high 1,6-selectivity in the presence of a cobalt catalyst (Table 1). Thus, the reaction of ethyl (2*E*,4*E*)-2,4-octadienoate (**1a**) with (triisopropylsilyl)acetylene (**2**) (2 equiv) in the presence of Co(OAc)₂·4H₂O (5 mol %), dppe (5 mol %), and zinc powder (50 mol %) in dimethyl sulfoxide (DMSO) at 80 °C for 20 h gave δ -alkynylated α,β -unsaturated ester **3a** in 83% yield (entry 1). This result prompted us to examine chiral bisphosphine ligands to achieve the asymmetric variant of this reaction. The reactions by use of chiral bisphosphine ligands, such as (*S,S*)-chiraphos, (*S,S*)-bdpp, (*R,R*)-dipamp, and (*R,R*)-QuinoxP*, proceeded to give the addition product **3a** in moderate to good yields, but they were ineffective in achieving high enantioselectivity (entries 2–5). On the other hand, the Duphos ligands **L1** ((*S,S*)-Me-Duphos) and **L2** ((*S,S*)-Et-Duphos) displayed high enantioselectivity to give **3a** with 88% and 96% ee, respectively (entries 6 and 7). The yield was slightly improved in a solvent system of DMSO/*t*-amyl alcohol (2:1) giving **3a** in 86% yield (entry 8). The yield and enantioselectivity of **3a** were kept high (88% yield, 97% ee) in the reaction with a reduced amount of zinc powder (10 mol %) (entry 9). The absolute configuration of **3a** obtained with (*S,S*)-Et-Duphos (**L2**) was determined to be *S* by analogy with (*S*)-**3c**.¹³

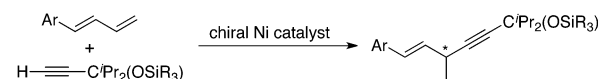
The results obtained for the cobalt-catalyzed 1,6-addition of (triisopropylsilyl)acetylene to dienoates and dienamides using **L2** or **L1** are summarized in Table 2.¹⁴ The reaction of dienoates **1a–1e** bearing substituents ("Pr, Et, Me, ^{*i*}Pr, CH₂OCH₂Ph) at the δ position gave the corresponding addition products **3a–3e** in good yields with high enantioselectivity (95–97% ee, entries 1–5). The addition to *tert*-butyl (**1f**) and phenyl (**1g**) esters proceeded well to give **3f** and **3g**

Scheme 1. Catalytic Addition of Terminal Alkynes

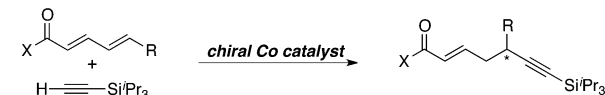
(a) Ru-catalyzed hydroalkynylation of 1,3-dienes (ref. 10)



(b) Ni-catalyzed asymmetric hydroalkynylation of 1,3-dienes (ref. 11)



(c) This work: Co-catalyzed asymmetric 1,6-addition to dienoates and dienamides



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Table 1. Cobalt-Catalyzed Asymmetric Alkynylation of $\alpha,\beta,\gamma,\delta$ -Unsaturated Ester **1a^a**

$\text{1a} + \text{H}-\text{C}\equiv\text{C}-\text{Si}^i\text{Pr}_3 \xrightarrow[\text{DMSO, 80 } ^\circ\text{C, 20 h}]{\text{Co(OAc)}_2\cdot 4\text{H}_2\text{O (5 mol \%), ligand (5 mol \%), Zn (50 mol \%)} } \text{3a}$

Ligands: (S,S)-chiraphos, (S,S)-bdpp, (R,R)-dipamp, (R,R)-QuinoxP*, (S,S)-Me-Duphos (L1), (S,S)-Et-Duphos (L2).
 R = Me: (S,S)-Me-Duphos (L1); R = Et: (S,S)-Et-Duphos (L2).

entry	ligand	yield (%) ^b	ee (%) ^c
1	dppe	83	—
2	(S,S)-chiraphos	90	26
3	(S,S)-bdpp	44 ^d	39
4	(R,R)-dipamp	80 ^d	19
5	(R,R)-QuinoxP*	63 ^d	75
6	(S,S)-Me-Duphos (L1)	92	88
7	(S,S)-Et-Duphos (L2)	81	96
8 ^e	(S,S)-Et-Duphos (L2)	86	96
9 ^{e,f}	(S,S)-Et-Duphos (L2)	88	97

^aReaction conditions: **1a** (0.20 mmol), **2** (0.40 mmol), Co(OAc)₂·4H₂O (5 mol %), ligand (5 mol %), Zn (50 mol %), DMSO (0.3 mL) at 80 °C for 20 h. ^bIsolated yield. ^cDetermined by chiral HPLC analysis. ^dIncluding other isomers (5–6%). ^eIn DMSO (0.2 mL) and *t*-amyl alcohol (0.1 mL). ^fZn (10 mol %) was used.

Table 2. Asymmetric Alkynylation of $\alpha,\beta,\gamma,\delta$ -Unsaturated Carbonyl Compounds^a

$\text{1} + \text{H}-\text{C}\equiv\text{C}-\text{Si}^i\text{Pr}_3 \xrightarrow[\text{DMSO, } t\text{-amyl alcohol, 80 } ^\circ\text{C, 20 h}]{\text{Co(OAc)}_2\cdot 4\text{H}_2\text{O (5 mol \%), L1 or L2 (5 mol \%), Zn (10 mol \%)} } \text{3}$

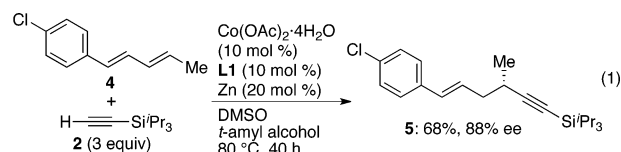
entry	ligand	X	R	yield (%) ^b	ee (%) ^c
1	L2	OEt	ⁿ Pr (1a)	88 (3a)	97
2	L2	OEt	Et (1b)	98 (3b)	96
3	L2	OEt	Me (1c)	81 (3c)	96
4	L1	OEt	ⁿ Pr (1d)	83 (3d)	97
5	L2	OEt	CH ₂ OCH ₂ Ph (1e)	83 (3e)	95
6 ^d	L2	O ^t Bu	ⁿ Pr (1f)	93 (3f)	98
7	L2	OPh	ⁿ Pr (1g)	99 ^e (3g)	95
8	L1	NPh ₂	ⁿ Pr (1h)	83 (3h)	95
9	L1	NPh ₂	Me (1i)	91 (3i)	88
10 ^f	L1	NPh ₂	^t Pr (1j)	65 (3j)	99

^aReaction conditions: **1** (0.20 mmol), **2** (0.40 mmol), Co(OAc)₂·4H₂O (5 mol %), ligand (5 mol %), Zn (10 mol %), DMSO (0.2 mL), *t*-amyl alcohol (0.1 mL) at 80 °C for 20 h. ^bIsolated yield of **3**. ^cDetermined by chiral HPLC analysis. ^dPerformed with alkynyl (0.60 mmol) for 40 h. ^eIncluding 2% of an isomer. ^fCo(OAc)₂·4H₂O (10 mol %), L1 (10 mol %), Zn (20 mol %) for 40 h.

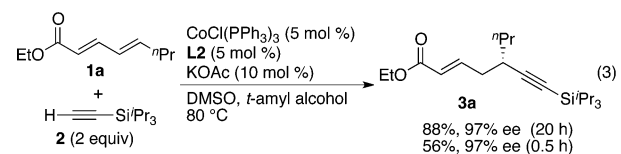
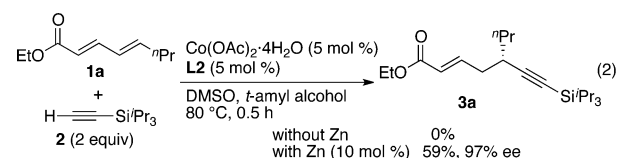
with 98% and 95% ee, respectively (entries 6 and 7). The present cobalt-catalyzed reaction can also be applied to dienamides **1h–1j** to give the corresponding δ -alkynylated

α,β -unsaturated amides **3h–3j** with high enantioselectivity (88–99% ee, entries 8–10). It should be noted that the 1,6-addition selectivity was very high, none of the 1,4-addition products being observed for any of the $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compound **1**.

The reaction of 1,3-diene **4** with (triisopropylsilyl)acetylene (**2**) in the presence of the Co/L1 (10 mol %) and Zn (20 mol %) also proceeded with very high regioselectivity to give δ -alkynylated α,β -unsaturated arene **5** in 68% yield with 88% ee (eq 1).

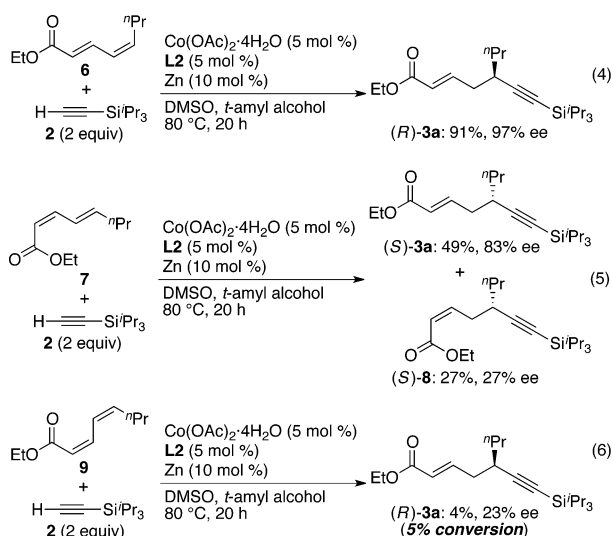


It is likely that the active catalytic species in the present reaction is a monovalent cobalt in situ generated by reduction of cobalt(II) acetate with zinc. Thus, no reaction was observed in the reaction of **1a** with **2** without zinc in a short reaction time of 0.5 h, while the addition proceeded in the presence of zinc to give **3a** in 59% yield (eq 2). It was also found that a

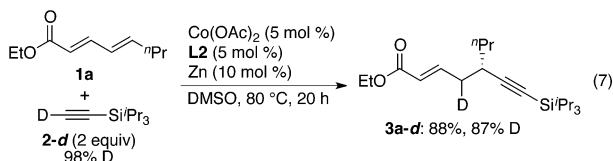


monovalent cobalt complex CoCl(PPh₃)₃ can be applied as a catalyst precursor without use of zinc and the reaction in the presence of L2 and KOAc for 20 h gave the addition product **3a** in 88% yield with 97% ee, where an apparent induction period was not observed: the reaction for 0.5 h gave 56% yield of **3a** (eq 3).¹⁵

A geometrical structure of the starting dienolate was found to affect both the absolute configuration of the product and reactivity of the dienolate. Thus, the addition of **2** to (2*E*,4*Z*)-**6** gave (*R*)-**3a** in 91% yield with 97% ee (eq 4), which is opposite in the absolute configuration to that obtained for (2*E*,4*E*)-**1a** (Table 2, entry 1). This result indicates that a mode of the enantioface selection on a γ,δ -unsaturated double bond is the same in both reactions of (2*E*,4*E*)-**1a** and (2*E*,4*Z*)-**6**. The reaction of (2*Z*,4*E*)-**7** gave (*S*)-(*E*)-**3a** in 49% yield with 83% ee, which has also the same absolute configuration as that obtained for (2*E*,4*E*)-**1a** (eq 5). The geometrical isomer (*S*)-(Z)-**8** was also formed in 27% yield with 27% ee. The formation of (*S*)-(*E*)-**3a** implies that the *cis*–*trans* isomerization of a π -allylcobalt intermediate takes place to give the stable *trans* isomer during the catalytic cycle (vide infra). On the other hand, the addition to (2*Z*,4*Z*)-**9** was very slow and the reaction gave only 4% yield of (*R*)-**3a** with 23% ee (eq 6). This low reactivity of dienolate (2*Z*,4*Z*)-**9**, which is difficult to adopt a cisoid conformation, may imply that η^4 -coordination of a cisoid diene moiety to an alkynylcobalt species is involved in the catalytic cycle.

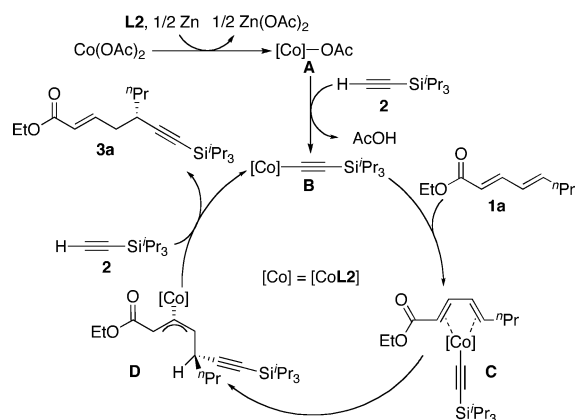


A deuterium-labeling experiment gave us information on the protonation step. Treatment of **1a** with deuterated alkyne **2-d** in place of **2** gave the addition product **3a-d**, which is deuterated at γ -position selectively (eq 7).¹⁶



On the basis of the results obtained in eqs 2–7, a catalytic cycle of the present reaction is proposed as illustrated in Scheme 2. The catalytic reaction is initiated by the reduction of

Scheme 2. Proposed Catalytic Cycle for the Cobalt-Catalyzed 1,6-Addition of **2 to **1a****



cobalt(II) to cobalt(I) by zinc powder giving cobalt(I) acetate **A**,¹⁷ which undergoes the reaction with a terminal alkyne to form alkynylcobalt(I)¹⁸ **B** and acetic acid. Coordination of dienophile **1a** to alkynylcobalt **B** with a cisoid diene moiety results in the formation of a (η^4 -diene)–cobalt complex **C**. Insertion of the diene into the alkynyl cobalt bond then gives π -allylcobalt **D**.¹⁹ Protonation of **D** at γ -position with the terminal alkyne **2** leads to the alkynylation product **3a** and regenerates the alkynylcobalt intermediate **B**.

In summary, we have developed a cobalt-catalyzed asymmetric 1,6-addition of (triisopropylsilyl)acetylene to

$\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds, which is realized by use of a cobalt/Duphos complex, giving δ -alkynylated α,β -unsaturated carbonyl compounds in high yields with very high regioselectivity and high enantioselectivity.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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(13) See the Supporting Information for details.

(14) In the reaction of phenylacetylene or 1-octyne, the addition products were not formed due to the alkyne oligomerization.

(15) The reaction in the absence of KOAc or **L2** did not proceed at all.

(16) The reaction was carried out with anhydrous $\text{Co}(\text{OAc})_2$ in the absence of *t*-amyl alcohol to avoid the incorporation of protons. The use of anhydrous $\text{Co}(\text{OAc})_2$ for the reaction of **1a** with **2** gave essentially the same yield and ee as that with $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (**3a** in 90% yield with 97% ee).

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