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Cobalt-Catalyzed Asymmetric 1,6-Addition of (Triisopropylsilyl)-acetylene to $\alpha,\beta,\gamma,\delta$-Unsaturated Carbonyl Compounds

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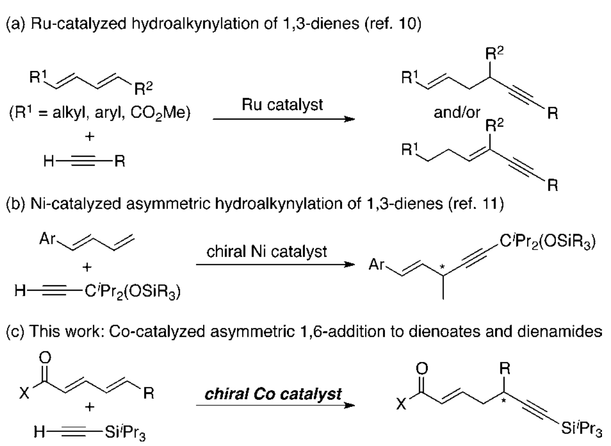
S Supporting Information

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 Pd[6] 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).

Scheme 1. Catalytic Addition of Terminal Alkynes



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 $Co(OAc)_2 \cdot 4H_2O$ (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 (^{n}Pr, Et, Me, ^{i}Pr, CH_2OCH_2Ph) 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**

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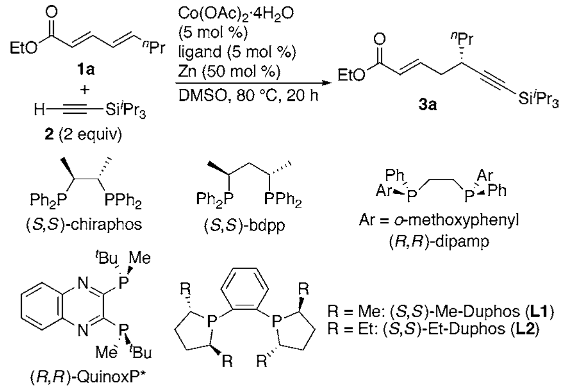
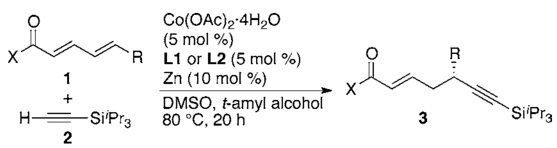
Table 1. Cobalt-Catalyzed Asymmetric Alkynylation of $\alpha,\beta,\gamma,\delta$-Unsaturated Ester 1a[a]



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

[a]Reaction conditions: **1a** (0.20 mmol), **2** (0.40 mmol), $Co(OAc)_2 \cdot 4H_2O$ (5 mol %), ligand (5 mol %), Zn (50 mol %), DMSO (0.3 mL) at 80 °C for 20 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Including other isomers (5–6%). [e]In DMSO (0.2 mL) and *t*-amyl alcohol (0.1 mL). [f]Zn (10 mol %) was used.

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

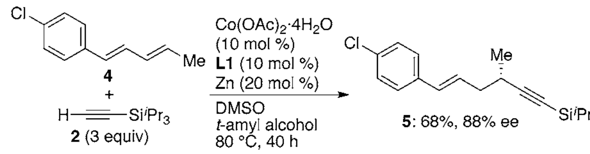


entry	ligand	X	R	yield (%)[b]	ee (%)[c]
1	**L2**	OEt	^{n}Pr (**1a**)	88 (**3a**)	97
2	**L2**	OEt	Et (**1b**)	98 (**3b**)	96
3	**L2**	OEt	Me (**1c**)	81 (**3c**)	96
4	**L1**	OEt	^{i}Pr (**1d**)	83 (**3d**)	97
5	**L2**	OEt	CH_2OCH_2Ph (**1e**)	83 (**3e**)	95
6[d]	**L2**	O^{t}Bu	^{n}Pr (**1f**)	93 (**3f**)	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	^{i}Pr (**1j**)	65 (**3j**)	99

[a]Reaction conditions: **1** (0.20 mmol), **2** (0.40 mmol), $Co(OAc)_2 \cdot 4H_2O$ (5 mol %), ligand (5 mol %), Zn (10 mol %), DMSO (0.2 mL), *t*-amyl alcohol (0.1 mL) at 80 °C for 20 h. [b]Isolated yield of **3**. [c]Determined by chiral HPLC analysis. [d]Performed with alkyne (0.60 mmol) for 40 h. [e]Including 2% of an isomer. [f]$Co(OAc)_2 \cdot 4H_2O$ (10 mol %), **L1** (10 mol %), Zn (20 mol %) for 40 h.

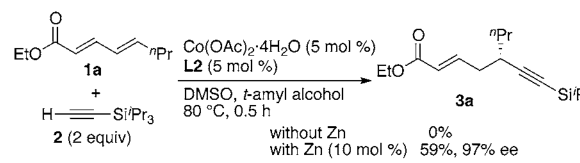
with 98% and 95% ee, respectively (entries 6 and 7). The present cobalt-catalyzed reaction can also be applied to dienamides **1h**–**1j** to give the corresponding δ-alkynylated α,β-unsaturated amides **3h**–**3j** with high enantioselectivity (88–99% ee, entries 8–10). It should be noted that the 1,6-addition 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).

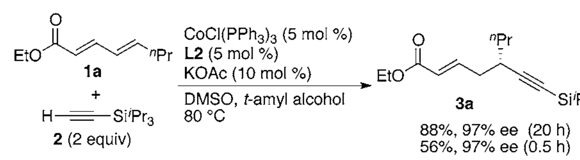


(1)

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



(2)



(3)

monovalent cobalt complex $CoCl(PPh_3)_3$ 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 dienoate was found to affect both the absolute configuration of the product and reactivity of the dienoate. 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 dienoate (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.

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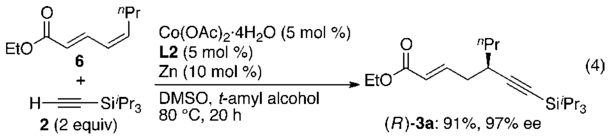
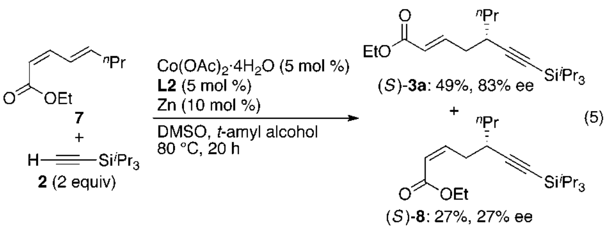
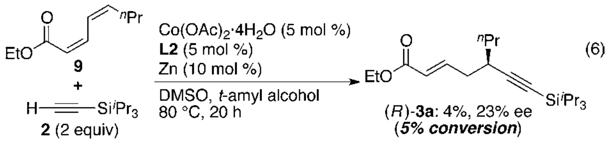
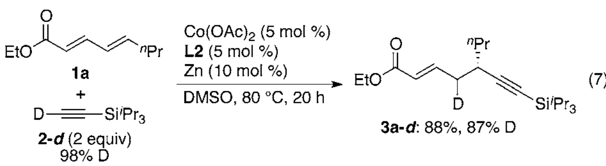




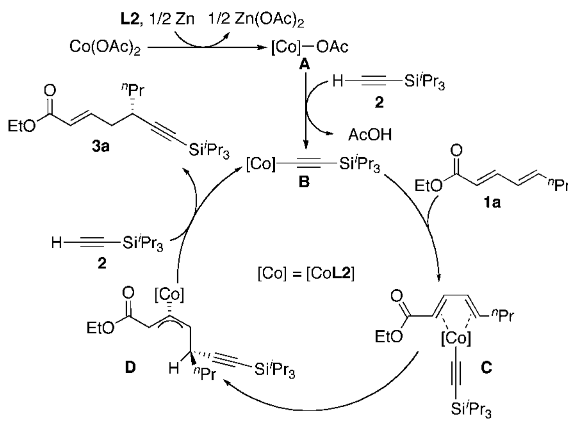


A deuterium-labeling experiment gave us information on the protonation step. Treatment of **1a** with deuterated alkyne **2-*d*** in place of **2** gave the addition product **3a–*d***, which is deuterated at γ-position selectively (eq 7).[16]



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 dienoate **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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■ REFERENCES

(1) For reviews, see: (a) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963. (b) Fujimori, S.; Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Boyall, D.; Carreira, E. M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1635.

(2) Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682.

(3) (a) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 10275. (b) Yazaki, R.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2011**, *13*, 952. (c) Yazaki, R.; Kumagai, N.; Shibasaki, M. *Chem. Asian. J.* **2011**, *6*, 1778.

(4) (a) Nishimura, T.; Guo, X.-X.; Uchiyama, N.; Katoh, T.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 1576. (b) Nishimura, T.; Sawano, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 8057. (c) Nishimura, T.; Sawano, T.; Tokuji, S.; Hayashi, T. *Chem. Commun.* **2010**, *46*, 6837. (d) Fillion, E.; Zorzitto, A. K. *J. Am. Chem. Soc.* **2009**, *131*, 14608.

(5) Nishimura, T.; Sawano, T.; Ou, K.; Hayashi, T. *Chem. Commun.* **2011**, *47*, 10142.

(6) Villarino, L.; Garcia-Fandiño, R.; López, F.; Mascareñas, J. L. *Org. Lett.* **2012**, *14*, 2996.

(7) For examples of asymmetric 1,4-addition of alkynylmetal reagents, see: (a) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3244. (b) Larionov, O. V.; Corey, E. J. *Org. Lett.* **2010**, *12*, 300. (c) Cui, S.; Walker, S. D.; Woo, J. C. S.; Borths, C. J.; Mukherjee, H.; Chen, M. J.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *132*, 436.

(8) For examples of transition metal-catalyzed asymmetric 1,6-addition of arylmetal reagents to $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl compounds, see: (a) Hayashi, T.; Yamamoto, S.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 4224. (b) Nishimura, T.; Yasuhara, Y.; Sawano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 7872. (c) Nishimura, T.; Noishiki, A.; Hayashi, T. *Chem. Commun.* **2012**, *48*, 973. For an example of diastereoselective 1,6-addition, see: (d) Okada, S.; Arayama, K.; Murayama, R.; Ishizuka, T.; Hara, K.; Hirone, N.; Hata, T.; Urabe, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6860.

(9) For examples of transition-metal catalyzed enantioselective 1,6-addition of alkylmetal reagents to $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl compounds and related compounds, see: (a) Fillion, E.; Wilsily, A.; Liao, E-T. *Tetrahedron: Asymmetry* **2006**, *17*, 2957. (b) den Hartog, T.; Harutyunyan, S. R.; Font, D.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 398. (c) Hénon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9122. (d) Wencel-Delord, J.; Alexakis, A.; Crévisy, C.; Mauduit, M. *Org. Lett.* **2010**, *12*, 4335. (e) den Hartog, T.; van Dijken, D. J.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron: Asymmetry* **2010**, *21*, 1574. (f) Tissot, M.; Müller, D.; Belot, S.; Alexakis, A. *Org. Lett.* **2010**, *12*, 2770. (g) Magrez, M.; Wencel-Delord,

J.; Alexakis, A.; Crévisy, C.; Mauduit, M. *Org. Lett.* **2012**, *14*, 3576. (h) Tissot, M.; Poggiali, D.; Hénon, H.; Müller, D.; Guénée, L.; Mauduit, M.; Alexakis, A. *Chem.—Eur. J.* **2012**, *18*, 8731.

(10) (a) Mitsudo, T.; Nakagawa, Y.; Watanabe, K.; Hori, Y.; Misawa, H.; Watanabe, H.; Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 565. (b) Mitsudo, T.; Hori, Y.; Watanabe, Y. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3201.

(11) Shirakura, M.; Suginome, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3827.

(12) For an example of cobalt-catalyzed asymmetric addition of silylacetylenes to oxa- and azabenzonorbornadienes, see: (a) Sawano, T.; Ou, K.; Nishimura, T.; Hayashi, T. *Chem. Commun.* **2012**, *48*, 6106. For an example of cobalt-catalyzed addition of terminal alkynes to iminium salts, see: (b) Chen, W.-W.; Bi, H.-P.; Li, C.-J. *Synlett* **2010**, 475.

(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 $Co(OAc)_2$ in the absence of *t*-amyl alcohol to avoid the incorporation of protons. The use of anhydrous $Co(OAc)_2$ for the reaction of **1a** with **2** gave essentially the same yield and ee as that with $Co(OAc)_2{\cdot}4H_2O$ (**3a** in 90% yield with 97% ee).

(17) The formation of a cobalt(I) species by reduction of a cobalt(II) complex with zinc is proposed in the cobalt-catalyzed reactions using cobalt(II) halides as catalyst precursors with zinc, see: (a) Jeganmohan, M.; Cheng, C.-H. *Chem.—Eur. J.* **2008**, *14*, 10876. (b) Gosmini, C.; Bégouin, J.-M.; Moncomble, A. *Chem. Commun.* **2008**, 3221.

(18) Albertin, G.; Antoniutti, S.; Bacchi, A.; Bordignon, E.; Pelizzi, G. *Organometallics* **1995**, *14*, 4126.

(19) For examples of π-allylcobalt(I) complexes, see: (a) Jonas, K. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 295. (b) Jonas, K. *J. Organomet. Chem.* **1990**, *400*, 165. (c) Bleeke, J. R.; Lutes, B. L.; Lipschutz, M.; Sakellariou-Thompson, D.; Lee, J. S.; Rath, N. P. *Organometallics* **2010**, *29*, 5057.