Enantioselective Addition of Terminal Alkynes to Aromatic Aldehydes Catalyzed by Copper(I) Complexes with Wide-Bite-Angle Chiral Bisphosphine Ligands: Optimization, Scope, and Mechanistic Studies

Yohsuke Asano, Hajime Ito, Kenji Hara, and Masaya Sawamura*

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan

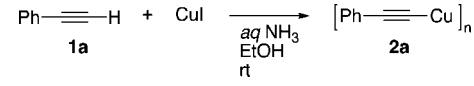
Received July 14, 2008

The addition of terminal alkynes to aromatic aldehydes was carried out in *t*-BuOH under mild conditions in the presence of a Cu-phosphine complex, which was prepared *in situ* from Cu(O-*t*-Bu) and TRAP chiral bisphosphine, to yield enantiomerically enriched propargyl alcohols with moderate enantioselectivities. Studies on the screening of various ligands showed that wide bite angles of bisphosphine ligands are important for the Cu catalysis. According to the analysis of stoichiometric reactions, the reaction presumably involves the nucleophilic addition of a TRAP-coordinated Cu(I) acetylide to an aldehyde: The alcoholic solvent participates in the addition through coordination to the Cu center and simultaneous protonation of the carbonyl oxygen. The C−C bond-forming addition step is reversible with a strong preference for the backward reaction.

Introduction

The addition of terminal alkynes to aldehydes serves as an important carbon−carbon bond formation reaction in the synthesis of complex organic molecules, because the resulting propargylic alcohols become versatile synthetic intermediates.[1] Conventionally, this process involves the conversion of the alkynes into the corresponding acetylide anions using a stoichiometric amount of a strong base. Given the recent demand for highly efficient and environmentally friendly processes, the direct alkynylation of aldehydes that avoids the use of a stoichiometric amount of a reagent has become highly desirable. While recent efforts on this subject have led to the discovery of various catalytic reactions that involve metal species such as Cs,[2] Zn,[3] In,[4] Ru−In,[5] Rh,[6] and Ag,[7] the catalysis of Cu is relatively unexplored. Although Cu is the first transition metal element that was shown to promote carbonyl alkynylations, the catalytic use of a Cu species was hampered by the low reactivity of Cu(I) acetylides.[8] Herein, we report the direct addition of terminal alkynes to aromatic aldehydes under mild conditions catalyzed by a Cu-phosphine complex, which was prepared *in situ* from Cu(O-*t*-Bu) and TRAP chiral bisphosphine,[9,10] to produce enantiomerically enriched propargyl alcohols with moderate enantioselectivities.[11,12] Furthermore, this is the first application of TRAP to Cu catalysis.

Scheme 1. Formation of Polymeric Cuprous Acetylide 2a



Results and Discussion

Catalyst Design. Copper acetylide is easily formed by the reaction of terminal alkynes and copper salts in weakly basic conditions. For example, the reaction of phenylacetylene (**1a**) and CuI in EtOH/NH_3(aq) forms polymeric cuprous phenylacetylide (**2a**) as an air- and water-stable, yellow solid (Scheme 1).[13] This polymer is so stable that it never attacks the C−O double bond of aldehydes (*Caution*: Metal acetylides are not shockproof and are potentially explosive).

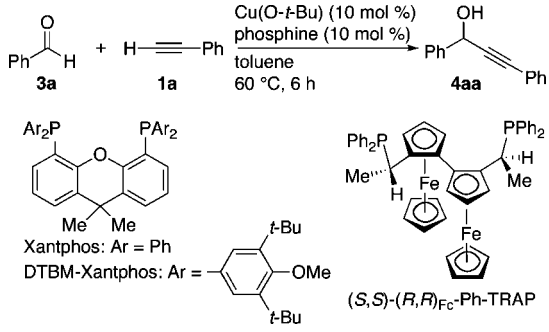
Recently, we have reported on the significant rate-accelerating effects of Xantphos ligands[14] in the Cu(I)-catalyzed dehydrogenative silylation of alcohols[15] and in the reaction of a diboron and allylic carbonates to produce allylboron compounds.[16] The high catalytic activities are attributable to the wide P−Cu−P

* Corresponding author. E-mail: sawamura@sci.hokudai.ac.jp.

(1) For reviews, see: (a) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095. (b) Pu, L. *Tetrahedron* **2003**, *59*, 9873.
(2) Tzalis, D.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1463.
(3) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687.
(4) (a) Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363. (b) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. J. *Am. Chem. Soc.* **2005**, *127*, 13760.
(5) Wei, C.; Li, C.-J. *Green Chem.* **2002**, *4*, 39.
(6) Dhondi, P. K.; Chisholm, J. D. *Org. Lett.* **2006**, *8*, 67.
(7) Yao, X.; Li, C.-J. *Org. Lett.* **2005**, *7*, 4395.
(8) Reppe, W. *Liebigs Ann. Chem.* **1955**, *596*, 25–32.
(9) For the synthesis, see: (a) Kuwano, R.; Sawamura, M. In *Catalysts for Fine Chemical Synthesis, Volume 5: Regio- and Stereo-Controlled Oxidations and Reductions*; Roberts, S. M., Whittall, J., Eds.; John Wiley & Sons: West Sussex, 2007; pp 73−86. (b) Sawamura, M.; Hamashima, H.; Sugawara, M.; Kuwano, R.; Ito, Y. *Organometallics* **1995**, *14*, 4549. (c) Kuwano, R.; Sawamura, M.; Okuda, S.; Asai, T.; Ito, Y; Redon, M.; Krief, A. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2807.
(10) For selected papers for the application of TRAP ligands, see: (a) Kuwano, R.; Kashiwabara, M. *Org. Lett.* **2006**, *8*, 2653. (b) Kuwano, R.; Sawamura, M.; Ito, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2571. (c) Kuwano, R.; Sawamura, M.; Shirai, J.; Takahashi, M.; Ito, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 485. (d) Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3309. (e) Goeke, A.; Sawamura, M.; Kuwano, R.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 662. (f) Sawamura, M.; Hamashima, H; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295.
(11) Part of this work has been published as a communication. See Asano, Y.; Hara, K.; Ito, H.; Sawamura, M. *Org. Lett.* **2007**, *9*, 3901.
(12) For a closely related work, see: Motoki, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 2997.
(13) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.
(14) (a) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081. (b) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895.

10.1021/om800667c CCC: $40.75
Publication on Web 10/14/2008

Table 1. Ligand Effect in the Cu-Catalyzed Addition of 1a to 3a[a]



entry	phosphine	NMR yield[b] (%)
1	none	0
2[c]	PPh_3	0
3	dppe	0
4	dppp	0
5	dppb	0
6	dppf	0
7	DPEphos	trace
8	DBEphos	2
9	Xantphos	10
10	DTBM-Xantphos	20
11	(*S*, *S*)-(*R*,*R*)$_{Fc}$-Ph-TRAP	77 (27% ee, *R*)

[a] **3a** (0.24−0.62 mmol, 1 M)/**1a**/Cu(O-*t*-Bu)/phosphine 1:2:0.1:0.1. [b] Unreacted **1a** and **3a** were quantitatively recovered. [c] **3a**/**1a**/Cu(O-*t*-Bu)/PPh_3 1:1:0.1:0.2.

bite angle that induces large distributions of active monomeric Cu species, such as (Xantphos)Cu−X [X = OR, H, $B(OR)_2$], in the aggregation equilibriums. Consequently, the results prompted us to examine large-bite-angle phosphines for the activation of Cu catalysis toward the addition of terminal alkynes and aldehydes via deaggregation of Cu acetylides.

Ligand Effect. A series of Cu(I)-phosphine catalysts were prepared *in situ* by mixing Cu(O-*t*-Bu) with phosphines (Table 1). Catalytic activities of the resulting Cu(I) complexes (10 mol %) were evaluated by the yields of propargylic alcohol **4aa** via reaction of benzaldehyde (**3a**) and phenylacetylene (**1a**, 2 equiv) in toluene at 60 °C for 6 h.

Reactions that involve Cu(O-*t*-Bu) alone or in combination with PPh_3 (Cu/P 1:2) or bisphosphines that possess an ordinary natural bite angle (such as dppe, dppp, dppb, and dppf) (Table 1, entries 1−6) were unsuccessful. In contrast, a slight conversion (10%) was observed when Xantphos was employed, suggesting the importance of a bite-angle effect (entry 9). Reactions that involved DPEphos[14a] and DBFphos,[14a,17] which are structurally related to Xantphos, showed traces of conversion (entries 7 and 8, respectively). The former is more flexible than Xantphos, and the latter never gives a monometallic chelate complex. Because a higher yield of **4aa** was obtained by introducing a bulky substituent in the *P*-phenyl groups of Xantphos (entry 10),[18] we can assume that the steric congestion around the metal center (a cone-angle effect) can also exert a beneficial effect for the deaggregation of the Cu acetylide in addition to the bite-angle effect. Accordingly, the use of (*S*,*S*)-(*R*,*R*)$_{Fc}$-Ph-TRAP chiral bisphosphines, which feature an extraordinarily large bite angle, resulted in a significantly higher yield of **4aa** (77%, entry 11). Furthermore, the enantiomeric excess of the product [27% ee (*R*)] indicated that the chirality of the (*S*,*S*)-(*R*,*R*)$_{Fc}$-Ph-TRAP ligand can exert some influence on the enantioselectivity of the addition reaction.

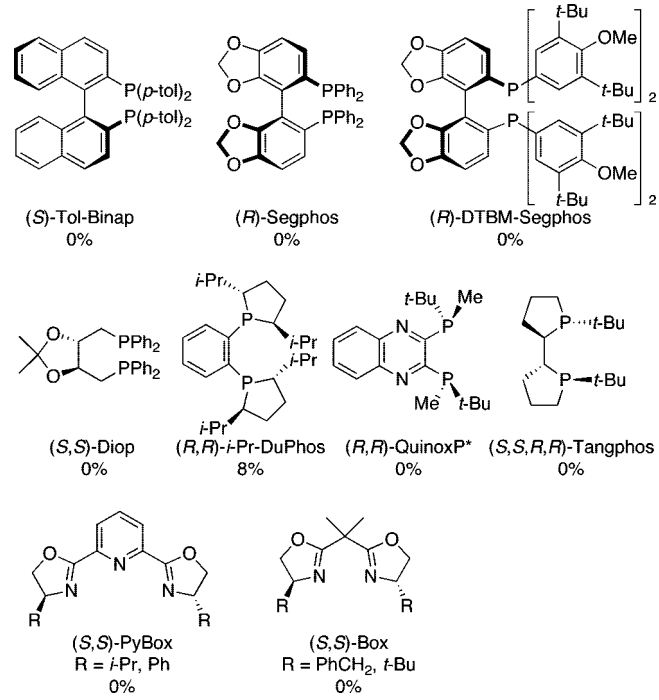


Figure 1. Summary of the screening of chiral ligands for the enantioselective addition of **1a** to **3a** (**3a**/**1a**/Cu(O-*t*-Bu)/ligand 1:2:0.1:0.1, toluene, 60 °C, 6 h). Yields of **4aa** are given below the structure of the ligands.

It should be noted that only DTBM-Xantphos and Ph-TRAP, which induced catalytic activities, gave a homogeneous, yellow solution under the reaction conditions (Table 1, entries 10, 11). Otherwise, the reaction mixture was heavily suspended with fluorecent yellow precipitates, implying the formation of unreactive, oligomeric copper(I) acetylides (entries 1−9).

Upon screening other chiral ligands that include bisphosphines with various backbone structures and *P*-substitution patterns as well as nitrogen-based ligands, our results revealed that most of the ligands are totally ineffective and that only the TRAP ligand exhibited a significant catalyst-activating effect (Figure 1).

We then examined various TRAP series of ligands with different substituents at phosphorus atoms under the conditions employed in the ligand screening (Table 2). The Cu-catalyzed reaction of **1a** and **3a** also proceeded with (*R*,*R*)-(*S*,*S*)$_{Fc}$-Bu-TRAP,[9c] which has flexible, electron-rich *P*-alkyl substituents (Bu groups), to afford propargylic alcohol **4aa** with 11% ee (*R*) in 36% yield (Table 3, entry 1). The yield is about a half of that with Ph-TRAP, and the enantioselectivity is significantly decreased. Use of the TRAP ligands (*p*-MeO-Ph-TRAP and *p*-Cl-Ph-TRAP)[9b] with *P*-aryl groups with either electron-donating or -withdrawing substituents resulted in a drastic drop of the yield, while the enantioselectivity was increased to some extent as compared with that with the parent Ph-TRAP ligand [*p*-MeO-Ph-TRAP, 35% ee (*R*); *p*-Cl-Ph-TRAP, 46% ee (*R*)] (entries 2 and 3). In order to enhance the acetylidede aggregation, we synthesized new TRAP derivatives, (*S*,*S*)-(*R*,*R*)$_{Fc}$-DTBM-TRAP and (*S*,*S*)-(*R*,*R*)$_{Fc}$-Terph-TRAP, with increased

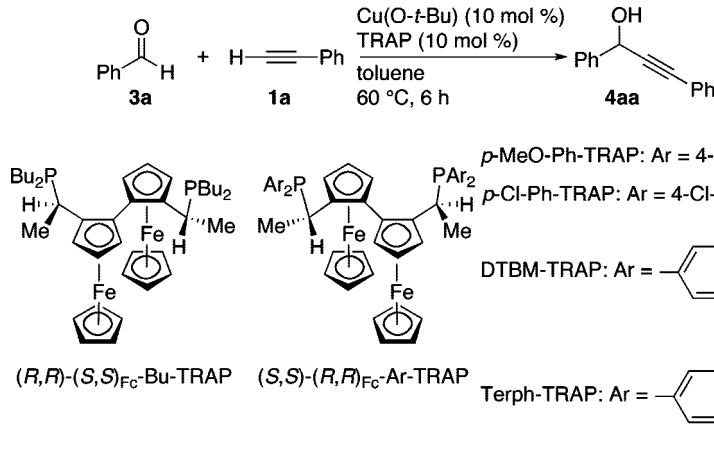
(15) (a) Ito, H.; Watanabe, A.; Sawamura, M. *Org. Lett.* **2005**, *7*, 1869 See also (Au catalysis): (b) Ito, H; Takagi, K.; Miyahara, T.; Sawamura, M. *Org. Lett.* **2005**, *7*, 3001.

(16) (a) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034. See also: (b) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856.

(17) Haenel, M. W.; Jakubik, D.; Rothenberger, E.; Schroth, G. *Chem. Ber.* **1991**, *124*, 1705.

(18) For the synthesis and use of DTBM-Xantphos, see ref 15a.

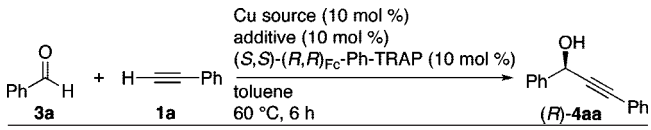
Table 2. Enantioselective Cu-Catalyzed Addition of 1a to 3a with Various TRAP Ligands[a]



entry	TRAP derivative	NMR yield[b] (%)	ee (%)
1	(R,R)-$(S,S)_{Fc}$-Bu-TRAP	36	11 (*R*)
2	(S,S)-$(R,R)_{Fc}$-*p*-MeO-Ph-TRAP	12	35 (*R*)
3	(S,S)-$(R,R)_{Fc}$-*p*-Cl-Ph-TRAP	6	46 (*R*)
4	(S,S)-$(R,R)_{Fc}$-DTBM-TRAP	19	2 (*R*)
5	(S,S)-$(R,R)_{Fc}$-Terph-TRAP	16	58 (*R*)

[a] **3a** (0.18−0.48 mmol, 1.0 M)/**1a**/Cu(O-*t*-Bu)/TRAP 1:2:0.1:0.1. [b] Unreacted **1a** and **3a** were quantitatively recovered.

Table 3. Effect of Cu Sources in the Cu(I)-Ph-TRAP-Catalyzed Addition of 1a to 3a[a]



entry	Cu source	additive	isolated yield (%)	ee (%)
1	$CuF_2 \cdot nH_2O$		0	
2	CuCl		0	
3	CuCl	KOH	44	40
4	CuBr		0	
5	CuBr	KOH	52	31
6	CuBr	$CsOH \cdot H_2O$	62	28
7	CuI		0	
8	CuOAc		0	
9	CuCN		0	
10	Cu_2O	KOH	40	30
11		K(O-*t*-Bu)	0	

[a] **3a** (0.21−0.47 mmol, 1.0 M)/**1a**/Cu source/additive/Ph-TRAP 1:2:0.1:0.1:0.1.

steric demand.[19] Unfortunately, however, these bulky ligands were much less efficient than Ph-TRAP in promotion of the Cu catalysis, while the change of the *P*-substituents from Ph to terphenyl groups showed marked impact on the improvement of the product enantiomeric excess [58% ee (*R*)] (entries 4 and 5). According to these results, we chose Ph-TRAP as a ligand for further studies for optimization of the reaction conditions toward higher catalytic activity and enantioselectivity.

Copper(I) Sources. Various copper sources were examined in combination with (S,S)-$(R,R)_{Fc}$-Ph-TRAP in the reaction of **1a** and **3a** under the conditions otherwise the same as those employed for the ligand screening (Table 3). The use of copper halides such as $CuF_2 \cdot nH_2O$, CuCl, CuBr, and CuI instead of Cu(O-*t*-Bu) resulted in no reaction (entries 1, 2, 4, and 7). Copper(I) acetate and cyanide were also totally ineffective (entries 8 and 9). It is considered that the copper complexes prepared from these copper sources lack the basisity required to initiate the reaction. When CuCl, CuBr, and Cu_2O were used together with KOH or $CsOH \cdot H_2O$ (CuBr/MOH 1:1), the reaction proceeded with a slower rate than that with Cu(O-*t*-Bu) to afford **4aa** with decreased yields (entries 3, 5, 6, and 10). The enantiomeric excess values of the product (28−40% ee) were almost the same or somewhat higher compared with that with Cu(O-*t*-Bu). When K(O-*t*-Bu) (10 mol %) was used in the absence of copper source, all the aldehyde (**1a**) was consumed to give a complex mixture without forming any trace of adduct **4aa** (entry 11).[20]

Solvents. To optimize the Cu-TRAP catalytic system, the conversion to **4aa** was carried out using various reaction solvents (60 °C, 6 h). Results are summarized in Table 4. Moderate conversions (66−74%) were observed in nonpolar hydrocarbon solvents such as toluene, benzene, and hexane (entries 1−3). The reaction in CH_2Cl_2 resulted in no conversion (entry 4). The reaction in aprotic, coordinative solvents such as THF and DMI was slower than that in toluene (entries 5 and 6). The reaction without using a solvent was as fast as that in toluene, while the enantioselectivity was significantly decreased (18% ee) (entry 7). The addition of water, in which neither the catalyst nor the substrates were soluble, showed virtually no effect on the yield and the enantiomeric excess of the product (entry 8).

As an obvious trend in the solvent screening, alcohols were more effective as solvents (Table 4, entries 9−17); furthermore, higher enatiomeric excesses of **4aa** corresponded to larger alcohols. Fluorinated alcohols such as CF_3CH_2OH and $(CF_3)_2CHOH$ drastically retarded or inhibited the reaction (entries 18 and 19). Based on entry 15, which afforded (*R*)-**4aa** with 42% ee in 91% yield, the optimal solvent was identified as *t*-BuOH.

(19) Procedures for the synthesis of DTBM-TRAP and Terph-TRAP are described in the Experimental Section.

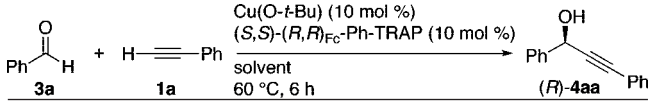
(20) For the catalysis of K(O-*t*-Bu) toward the addition of terminal alkynes to ketones, see: Babler, J. H.; Liptak, V. P.; Phan, N. *J. Org. Chem.* **1996**, *61*, 416.

(21) Togni, A.; Breutel, C.; Schnyder, F.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062.

(22) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 3212.

(23) Sturm, T.; Xiao, L.; Weissensteiner, W. *Chimia* **2001**, *55*, 688.

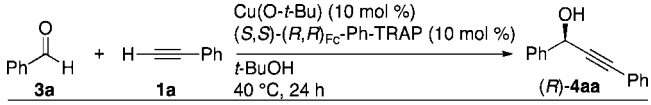
Table 4. Solvent Effect in the Enantioselective Cu-Catalyzed Addition of 1a to 3a[a]



entry	solvent	isolated yield[b] (%)	ee (%)
1	toluene	74	27
2	benzene	69	23
3	hexane	66	13
4	CH_2Cl_2	0	–
5	THF	50	33
6	DMI	24	31
7	none	76	18
8	H_2O	65	18
9	MeOH	91	25
10	EtOH	94	27
11	$PhCH_2OH$	84	24
12	$Me_3CCH_2CH_2OH$	74	27
13	*i*-PrOH	87	32
14	$(i\text{-Pr})_2CHOH$	81	36
15	*t*-BuOH	91	42
16	$CH_3CH_2CMe_2OH$	80	35
17	$Me_2C(OH)CMe_2OH$	81	30
18	CF_3CH_2OH	4	11
19	$(CF_3)_2CHOH$	0	–

[a] **3a** (0.21−0.62 mmol, 1 M)/**1a**/Cu(O-*t*-Bu)/Ph-TRAP 1:2:0.1:0.1. [b] Unreacted **3a** and **1a** were quantitatively recovered.

Table 5. Effect of Concentration and Stoichiometry in the Enatioselective Cu-Catalyzed Addition of 1a to 3a at 40 °C



entry	conc of **3a** (M)	**1a**/**3a**	isolated yield[a] (%)	ee (%)
1	1.0	2.0	54	46
2	0.50	2.0	87	51
3	0.25	2.0	73	48
4	0.50	1.1	79	49
5	0.50	1.5	81	49
6	0.50	3.0	88	51
7	0.50	5.0	78	51

[a] Unreacted **1a** and **3a** were quantitatively recovered.

Temperature, Substrate Stoichiometry, and Concentration. We further investigated the detailed reaction conditions on reaction temperature, substrate stoichiometry, and concentration for the conversion of **1a** and **3a** into **4aa**. Results are summarized in Table 5. When the reaction temperature was decreased from 60 to 40 °C under the conditions that were otherwise the same as employed in Table 4, entry 15, the reaction mixture became a suspension with fluorescent yellow precipitates. The reaction that was carried out for 24 h gave **4aa** with slightly improved enantiselectivity (46%) but with lower yield (54%) (Table 5, entry 1). When the concentration of **3a** was reduced to 0.5 M, the precipitation was reduced, and the reaction was faster than that under the 1.0 M conditions. As a result, the yield of **4aa** recovered to 87%, and at the same time the enantiomeric excess of **4aa** was further increased to 51% ee (entry 2). Further decrease of the concentration to 0.25 M, however, resulted in the decrease of both the yield and the enantiomeric excess value (73%, 48% ee) (entry 3).

Next, we examined the effect of the amount of alkyne **1a** relative to **3a** with the constant loading of the latter. The comparison of entries 2, 4, and 5 in Table 5 shows that the decrease of the amount of alkyne **1a** to 1.1 equiv and **3a** to 1.5 equiv caused only slight decreases in both the yield and the enantioselectivity. On the other hand, the increase of the amount of **1a** from 2.0 equiv to 3.0 equiv caused virtually no effect in both the yield and the selectivity (entry 6). Further increase of **1a** to 5.0 equiv lowered the yield of **4aa**, while the enantiomeric excess value was constant (entry 7).

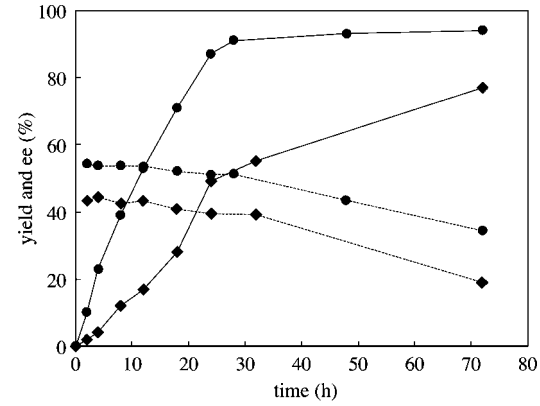


Figure 2. Plots of isolated yields (lines) and ee values (dashed lines) of **4aa** versus reation times for the enatioselective Cu-catalyzed addition of **1a** to **3a** at 40 °C in toluene (◆) and *t*-BuOH (●). **3a** (0.20−0.23 mmol, 0.5 M)/**1a**/Cu(O-*t*-Bu)/Ph-TRAP 1:2:0.1:0.1.

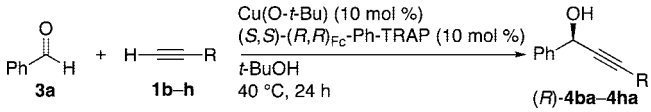
Racemization and Reversibility of the Addition Reaction. During the course of this study, we noticed that the enantiomeric excess of the propargylic alcohol (**4aa**) dropped significantly when a prolonged reaction time was applied. Accordingly, to observe how the catalytic reaction changes with time, the yield and enantiomeric excess of propargylic alcohol **4aa** were followed. Figure 2 shows time profiles of the conversion of **1a** and **3a** into **4aa** catalyzed by Cu(O-*t*-Bu)-(*S*,*S*)-(*R*,*R*)$_{Fc}$-Ph-TRAP on the yield and enantiomeric excess value of **4aa**. To see the solvent effect, both toluene and *t*-BuOH were examined.

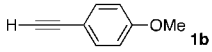
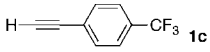
The adduct **4aa** was gradually formed without an induction period in both solvents; however, the ways of increase of **4aa** were different depending on the solvents especially in the earlier stage of the reaction. It could be attributed to the fact that the initial stage of the reaction in toluene is short of alcohol, which is able to accelerate the addition reaction.

A decrease in the enantiomeric excess of **4aa** was observed even in the initial stage of the reaction in both solvents. The decreasing rate of the enantiomeric excess was slightly faster in toluene solvent. Importantly, the decrease in enantiomeric excess in *t*-BuOH continued even after the yield reached almost the maximum value. This clearly indicates that the enantiomerically enriched propargylic alcohol (**4aa**) once formed undergoes racemization under the reaction conditions. No decrease in the enantiomeric excess was observed when **4aa** with 49.6% ee in *t*-BuOH was heated at 40 °C for 48 h. Therefore, the Cu-Ph-TRAP complex is the cause of the racemization. These results suggest that the racemization may be due to an equilibrium between the two enantiomers of **4aa** through reverse reactions that convert the enantiomeric propargylic alcohols into their precursors such as aldehyde **3** and cuprous acetylides (*vide infra*).

Effect of Alkynes. The influence of various alkyne substrates on the reactivity and enantioselectivity was examined using the reaction with **3a** under constant conditions (10 mol % Cu-(*S*,*S*)-(*R*,*R*)$_{Fc}$-Ph-TRAP, [**3a**] = 0.5 M in *t*-BuOH, **3a**/**1**, 1:2.0, 40 °C, 24 h). Results are summarized in Table 6. Whereas the electron-donating *p*-MeO substituent on the aromatic ring of phenylacetylene (entry 1) slightly increased the yield without affecting the enantiomeric excess value, the substitution with

Table 6. Enantioselective Cu-Catalyzed Addition of Various Alkynes (1) to 3a[a]



entry	alkyne	product	isolated yield (%)	ee (%)
1	 **1b**	**4ba**	92	48
2	 **1c**	**4ca**	37	45
3	H—≡—Bu **1d**	**4da**	83	41
4	H—≡—*i*-Pr **1e**	**4ea**	32	43
5	H—≡—*t*-Bu **1f**	**4fa**	7	N.D.
6	H—≡—$SiMe_3$ **1g**	**4ga**	8	36
7	H—≡—CO_2Et **1h**	**4ha**	0	–

[a] **3a** (0.20−0.22 mmol, 0.5 M)/**1**/Cu(O-*t*-Bu)/Ph-TRAP 1:2:0.1:0.1.

the electron-withdrawing *p*-CF_3 (entry 2) group resulted in a substantial drop in the yield and in the slight decrease in the enantioselectivity. For the reactions of aliphatic alkynes **1d**−**f**, our catalytic system was also effective; however, drastically lower yields were observed with increasing α-branching of the alkyl substituent (entries 3−5). Poor yields were obtained for the reactions of trimethylsilylacetylene (**1g**, entry 6), and no reaction occurred with ethoxycarbonylacetylene (**1h**, entry 7). Thus, the alkynes with more electron-donating substituents showed higher reactivity and caused a faster reaction. Therefore, it can be said that the higher the electron density and the nucleophilicity of the metalated sp-carbon atom of the acetylides, the faster the overall reaction.

Effect of Aldehydes. Next, the effect of various aldehydes on the reactivity and enantioselectivity were examined using the reaction with phenylacetylene (**1a**) under constant conditions (10 mol % Cu-(*S*,*S*)-(*R*,*R*)$_{Fc}$-TRAP, [**3**] = 0.5 M in *t*-BuOH, **3**/**1a**; 1:2.0, 40 °C, 24 h). Results are summarized in Table 7. As shown in entries 1−3, 6, and 7, electron-donating substituents (alkyl, −OMe) on the *para*- and *meta*-positions of aromatic aldehydes decreased the reactivity along with slightly positive effects on the enantioselectivity. On the other hand, as shown in entries 4, 5, and 8, electron-withdrawing groups on the *para*-(−Cl, −F) and *meta*-positions (−CO_2Me) enhanced the reactivity with slightly negative effects on the selectivity. It is noteworthy that an *o*-Me group (entries 9, 10) showed activating effects with a slightly negative effect on the selectivity, whereas a bulky phenyl group in the same position caused overcrowded conditions (entry 11). Similar steric effects were also observed between the isomeric naphthaldehydes (entries 12, 13). In the cases of aliphatic aldehydes such as **3o** and **3p**, the Cu-TRAP catalyst did not exhibit any activity (entries 14, 15). Overall, it is an obvious trend that the higher the electrophilicity of the aldehydes (**3**), the faster the catalytic reaction, while the effects of the *ortho*-substituents are puzzling.

^{31}P NMR and CSI-MS Studies for Phosphine/Cu/Alkyne Mixtures. To gain insight into the nature of the Cu-TRAP species, NMR spectroscopy was performed with various combinations of phosphine ligands, copper species, and phenylacetylene (**1a**). Figure 3 shows results obtained with the Ph-TRAP ligand. A yellow, homogeneous mixture of equimolar amounts of Ph-TRAP and Cu(O-*t*-Bu) in C_6D_6 showed several broad signals in the ^{31}P NMR spectrum (Figure 3B) including a signal that corresponds to uncoordinated Ph-TRAP (see Figure 3A). Upon addition of **1a** (1 equiv), the yellow color intensified, while the ^{31}P NMR signals converged into a major singlet (δ 10.1) (Figure 3C). Based on the similarity to that of species obtained from $[CuC{\equiv}CPh]_n$ and Ph-TRAP (Cu:TRAP 1:1, 60 °C, 3 h, Figure 3D), the major signal was assigned to the TRAP-coordinated Cu(I) acetylide species "Cu(η^1-C≡CPh)(η^2-Ph-TRAP)" (**5a**), while we are yet unsuccessful in determining unambiguously whether it is monomeric or not (*vide infra*). The chemical shift and the line width of the signal for **5a** were kept constant regardless of shortage or excess of Ph-TRAP relative to Cu of $[CuC{\equiv}CPh]_n$ (Ph-TRAP/Cu 0.6:1 and 2:1, Figure 3E, F).[24]

All attempts to isolate cuprous acetylide-TRAP complexes of the type **5** have failed. Our attempts of recrystallization of **5** resulted in the complete loss of the acetylide fragment. This is in sharp contrast to the results reported by Gimeno et al.:[24] They successfully isolated and characterized several dimeric cuprous acetylides [Cu_2(μ- η^1-C≡CR)$_2$(μ-dppf)] (R = aryl or alkyl) as air-stable solids. This may be in accordance with the superiority of Ph-TRAP in activation of the copper catalysis over other ligands.

In order to elucidate the structure of **5a**, we performed cold spray ionization mass (CSI-MS) spectroscopy at −30 °C for the solution for Figure 3D, which was diluted with CH_3CN/MeOH (1:1) before measurement. As shown in Figure 4, however, molecular ion peaks that correspond to "monomeric" **5a** were not observed. Instead, signals that can be ascribed to $[Cu(Ph\text{-}TRAP)]^+$ were observed as main peaks at m/z = 857.09 (Figure 4B) together with weak signals that are assignable to those from a dimeric complex $[\{Cu(C{\equiv}CPh)(Ph\text{-}TRAP)\}_2 + CH_3CN + Na]^+$ at m/z = 1982.28 (Figure 4C).[25] Other fragment ion peaks with m/z values smaller than that for $[Cu(Ph\text{-}TRAP)]^+$ were also observed. This result raises two possibilities for the structure and nature of **5a**. One is as follows: **5a** exists mostly as a dimer $[Cu(C{\equiv}CPh)(Ph\text{-}TRAP)]_2$ in the solution, and the dimeric form is more reactive (unstable) than the reported copper acetylide dimers with an "ordinary" bidentate phosphine ligand. Even if the fragmentation of the dimer under the ionization conditions caused the release of a monomer [Cu(η^1-C≡CPh)(η^2-Ph-TRAP)], it would be more reactive than the dimer and hence further degrade to the acetylide-free ion $[Cu(Ph\text{-}TRAP)]^+$. The second possible explanation is as follows: Monomeric **5a** [Cu(η^1-C≡CPh)(η^2-Ph-TRAP)] is a major component in the solution and is less stable than the dimer $[Cu(C{\equiv}CPh)(Ph\text{-}TRAP)]_2$, which exists as a minor component, and hence, upon ionization, the former encountered complete fragmentation to form the $[Cu(Ph\text{-}TRAP)]^+$ ion and other fragment ions, while the latter formed molecular ion peaks as an adduct with the solvent and sodium cation.

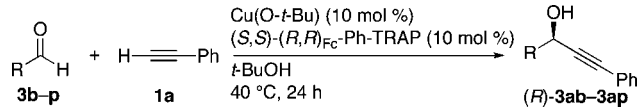
Reactivity of Ph-TRAP-Cuprous Acetylide Complex toward Aldehyde. Figure 5A shows the ^{1}H NMR spectrum of Ph-TRAP-cuprous phenylacetylide complex **5a**, which was

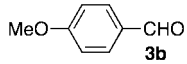
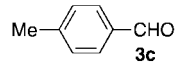
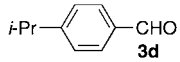
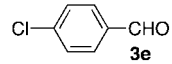
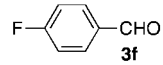
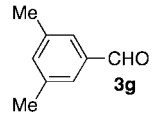
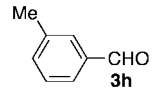
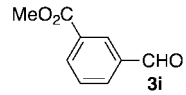
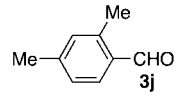
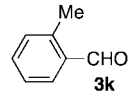
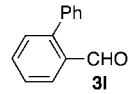
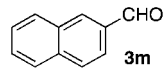
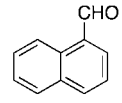
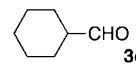
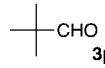
(24) In contrast, when the same set of NMR measurements were conducted with Xantphos ligand, the signal for a complex that appeared after the addition of **1a** was broad, and the significant signal for uncoordinated Xantphos remained. When *i*-Pr-DUPHOS was used as a ligand, two broad peaks were observed in the low magnetic field (see Supporting Information for NMR spectra).

(25) Díez, J.; Gamasa, M. P.; Gimeo, J.; Aguirre, A.; García-Granda, S.; Holubova, J.; Falvello, L. R. *Organometallics* **1999**, *18*, 662.

(26) A reviewer pointed out the ambiguity of the assignment of this signal.

Table 7. Enantioselective Cu-Catalyzed Addition of 1a to Various Aldehydes (3)[a]



entry	aldehyde	product	isolated yield[b] (%)	ee (%)
1	 3b	**3ab**	18	56
2	 3c	**3ac**	38	54
3	 3d	**3ad**	48	55
4	 3e	**3ae**	93	43
5	 3f	**3af**	92	51
6	 3g	**3ag**	55	56
7	 3h	**3ah**	73	52
8	 3i	**3ai**	99	48
9	 3j	**3aj**	53	47
10	 3k	**3ak**	92	45
11	 3l	**3al**	63	39
12	 3m	**3am**	8	54
13	 3n	**3an**	82	54
14	 3o	**3ao**	0	–
15	 3p	**3ap**	0	–

[a] **3** (0.2−0.22 mmol, 0.5 M)/**1a**/Cu(O-*t*-Bu)/Ph-TRAP 1:2:0.1:0.1. [b] Unreacted aldehyde **3** and alkyne **1a** were quantitatively recovered.

prepared from Ph-TRAP, Cu(O-*t*-Bu), and phenylacetylene (**1a**) in C_6D_6 as shown above (the solution for Figure 5C). This solution involved 1 equiv of *t*-BuOH, which was formed upon the deprotonation of **1a** with the alkoxide. This solution was treated with PhCHO (**3a**) (1 equiv) and heated at 60 °C for 15 h. According to the ^{1}H NMR spectrum (Figure 5B), no propargylic alcohol **4aa** was formed, and both complex **5a** and the aldehyde **3a** were intact. Furthermore, changes in the spectrum were not observed even upon addition of 5 equiv of *t*-BuOH (as a possible proton source) and heating at 60 °C for an additional 3 h (except for the increased *t*-BuOH signals) (Figure 5C). Propargylic alcohol **4aa** was produced when the mixture was treated with 19 equiv of phenylacetylene (**1a**) (56% conversion based on **3a**, 60 °C, 14 h) (Figure 5D). Throughout

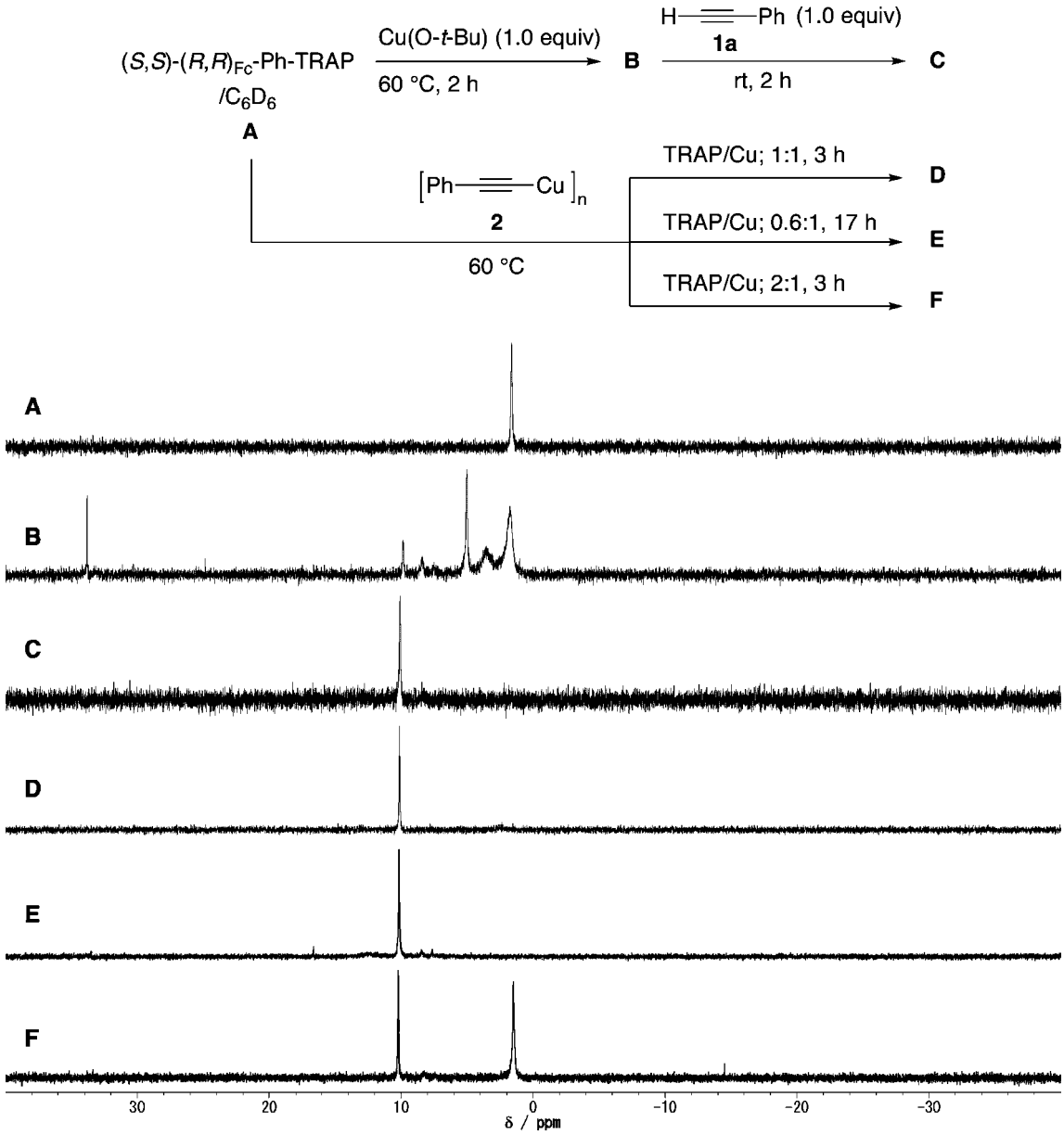


Figure 3. ^{31}P NMR spectra of (*S*,*S*)-(*R*,*R*)$_{Fc}$-Ph-TRAP and its Cu derivatives in C_6D_6.

these experiments and during the addition reaction, the ^{31}P NMR monitoring kept on showing the sharp peak at δ 10.1 that corresponded to Ph-TRAP-cuprous acetylide complex **5a** as the main signal.

NMR Observation of Reverse Reaction of Propargylic Alcohol. A proof of the reversibility of the reaction of Ph-TRAP-cuprous acetylide complex **5** and aldehyde **3** to form propargylic alcohol **4** (via a cuprous alkoxide), which was suggested by the racemization of **5a** (Figure 2), was obtained by the observation of a stoichiometric C−C bond-breaking reaction of propargylic alcohol **4aa**. Thus, **4aa** was reacted with a mixture of Ph-TRAP and Cu(O-*t*-Bu) in C_6D_6, and the reaction was monitored by ^{1}H and ^{31}P NMR spectroscopies (Figure 6). The C−C bond-breaking reaction occurred at ambient temperature: The signals for **4aa** (Figure 6A) completely disappeared within 2 h, and new signals for PhCHO (**3a**, δ 9.63 and others) and *t*-BuOH (δ 1.09) appeared instead (Figure 6B). The ^{31}P NMR spectrum suggested that several copper species were formed, the major species being cuprous acetylide **5a** (δ 10.1) (Figure 6E). After heating at 60 °C for 3 h, the signals of **4aa** did not appear again in the ^{1}H NMR spectrum (Figure 6C), and the ^{31}P NMR signal that corresponds to **5a** became larger (Figure 6F). Further heating of the mixture for 9 h caused no change in the ^{1}H NMR signals for **3a** but resulted in sharpening of some other peaks (Figure 6D). In the ^{31}P NMR spectrum, the signals for cuprous acetylide **5a** became more pronounced (Figure 6G).

Combining the results of the monitoring of racemization (Figure 2) and the NMR experiments for the reverse reaction (Figure 6), it can be concluded that the C−C bond-forming step in the addition of Ph-TRAP cuprous acetylide complex **5** to aldehyde **3** is reversible with a strong preference for the C−C bond-breaking backward reaction. However, the addition reaction of alkynes and aldehydes to form propargylic alcohols is highly exothermic (**1a** + HCHO, HF3-21G: −20.8 kcal mol^{-1}). Moreover, the protonation of the cuprous alkoxide with the terminal alkyne should be irreversible. Therefore, it is reasonable that the formation of the propargylic alcohol **4** can proceed in the presence of terminal alkyne **1** regardless of the strong backward nature of the C−C bond-forming reaction.

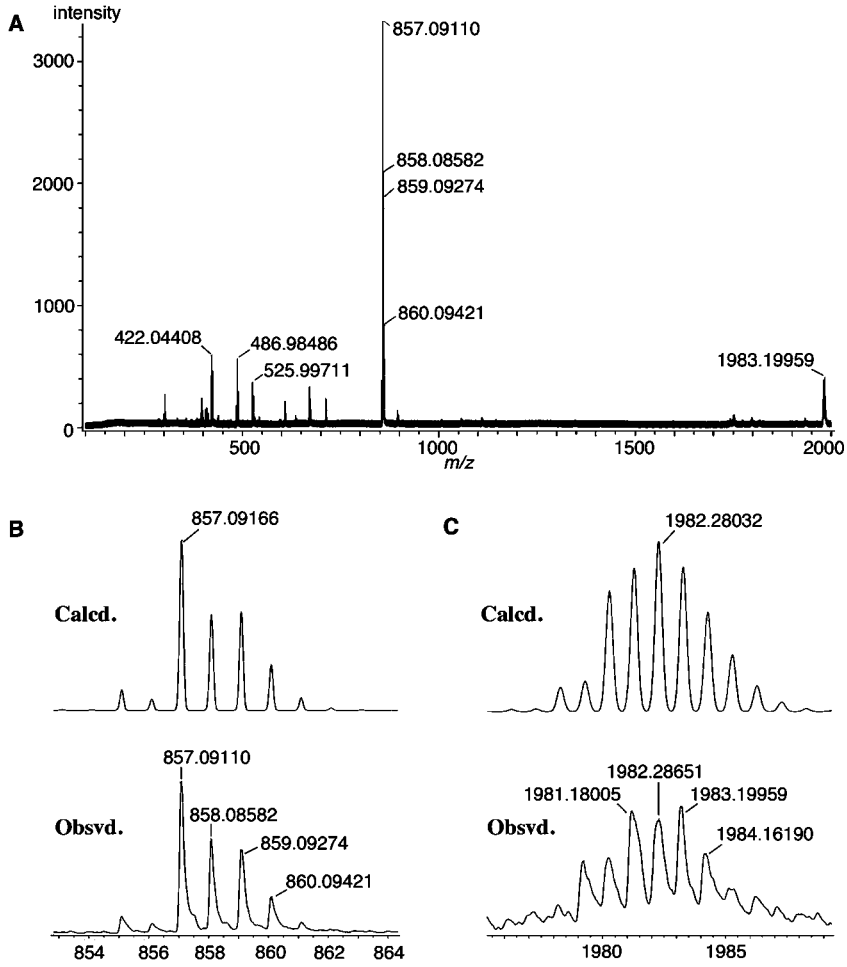


Figure 4. CSI(+)-MS (−30 °C) spectrum of the solution that was obtained by diluting the solution D in Figure 3 (Ph-TRAP/$[Cu(C{\equiv}CPh)]_n$ (**2a**) 1:1 in C_6D_6) with CH_3CN/MeOH (1:1). (A) Spectrum in a full *m*/*z* range. (B) Expanded spectrum that shows monomeric fragment $[Cu(Ph\text{-}TRAP)]^+$ (*m*/*z* 857.0911) with the peak distribution calculated for $C_{48}H_{44}CuFe_2P_2$ (*m*/*z* 857.0917). (C) Expanded spectrum that shows the dimeric adduct ion $[\{Cu(C{\equiv}CPh)(Ph\text{-}TRAP)\}_2{+}CH_3CN{+}Na]^+$ (*m*/*z* 1982.2865) with the peak distribution calculated for $C_{114}H_{101}Cu_2Fe_4P_4NaN$ (*m*/*z* 1982.2803).

Proposed Mechanisms. So far, we have obtained no proof that indicates whether **5a** exists in a monomeric form or a dimeric form; however, according to the specific observation of the TRAP-coordinated Cu^+ ion $[Cu(Ph\text{-}TRAP)]^+$ in the CSI-mass spectroscopy (*vide infra*), we would prefer tentatively the monomeric form as a catalytically active species that reacts with an aldehyde. Furthermore, on the basis of the results of the NMR experiments, two possible reaction pathways may be assumed. One proceeds via cuprous propargylic alkoxide **6** (Scheme 2), and the other via the direct formation of propargylic alcohol **4** from cuprous acetylide **5**, which is assisted by protonation of the carbonyl oxygen with an external alcohol (Scheme 3).[27] The latter can explain the effect of the alcoholic solvents on the rate enhancement and the enantioselectivity.

In the first pathway (Scheme 2), cuprous propargylic alkoxide **6** is formed from acetylide **5** and aldehyde **3** through a reversible process with a strong preference for the starting materials. Next, propargylic alcohol **4** is formed through metathesis between cuprous alkoxide **6** and alkyne **1**, which is irreversibly driven by the stability of cuprous acetylide **5**.

In the second pathway (Scheme 3), an alcohol participates in the nucleophilic addition of cuprous acetylide **5** to aldehyde **3** through coordination to the Cu center and simultaneous protonation of the carbonyl oxygen, releasing propargylic alcohol **4** with the formation of cuprous alkoxide **7**. After that, alkoxide **7** reacts with alkyne **1** irreversibly to reproduce cuprous acetylide **5**.

Conclusions. We demonstrated the catalytic activity of a Cu(I) complex with TRAP chiral bisphosphine for the direct addition of terminal alkynes to aldehydes to produce enantiomerically enriched propargyl alcohols, under mild conditions, with moderate enantioselectivities. Furthermore, our studies on the screening of various ligands showed that wide bite angles of bisphosphine ligands are important for the Cu catalysis and that the Ph-TRAP ligand is most effective. Insight into the reaction mechanism was gained via stoichiometric reactions and may help in the design of more advanced catalysts.

Experimental Section

General Comments. All manipulations involving air- and moisture-sensitive compounds were carried out under argon. NMR spectra were recorded on a Varian Gemini 2000 (^1H, 300 MHz; ^{13}C, 75.4 MHz; ^{31}P, 121.4 MHz) spectrometer. Tetramethylsilane and $CDCl_3$ were used as internal standards in the ^1H and ^{13}C NMR spectroscopies, respectively. In the ^{31}P NMR spectroscopy, 85% phosphoric acid was employed as an external standard. High-performance liquid chromatography (HPLC) was performed with a Daicel CHIRALCEL OD-H (Daicel, 0.46 cm × 25 cm) column on a Shimadzu LC-6A to determine the enantiomer excess of propargylic alcohols (flow rate: 0.5 or 1.0 mL/min, eluent: *i*-PrOH/

(27) A reviewer suggested a possibility of [2 + 2] cycloaddition.

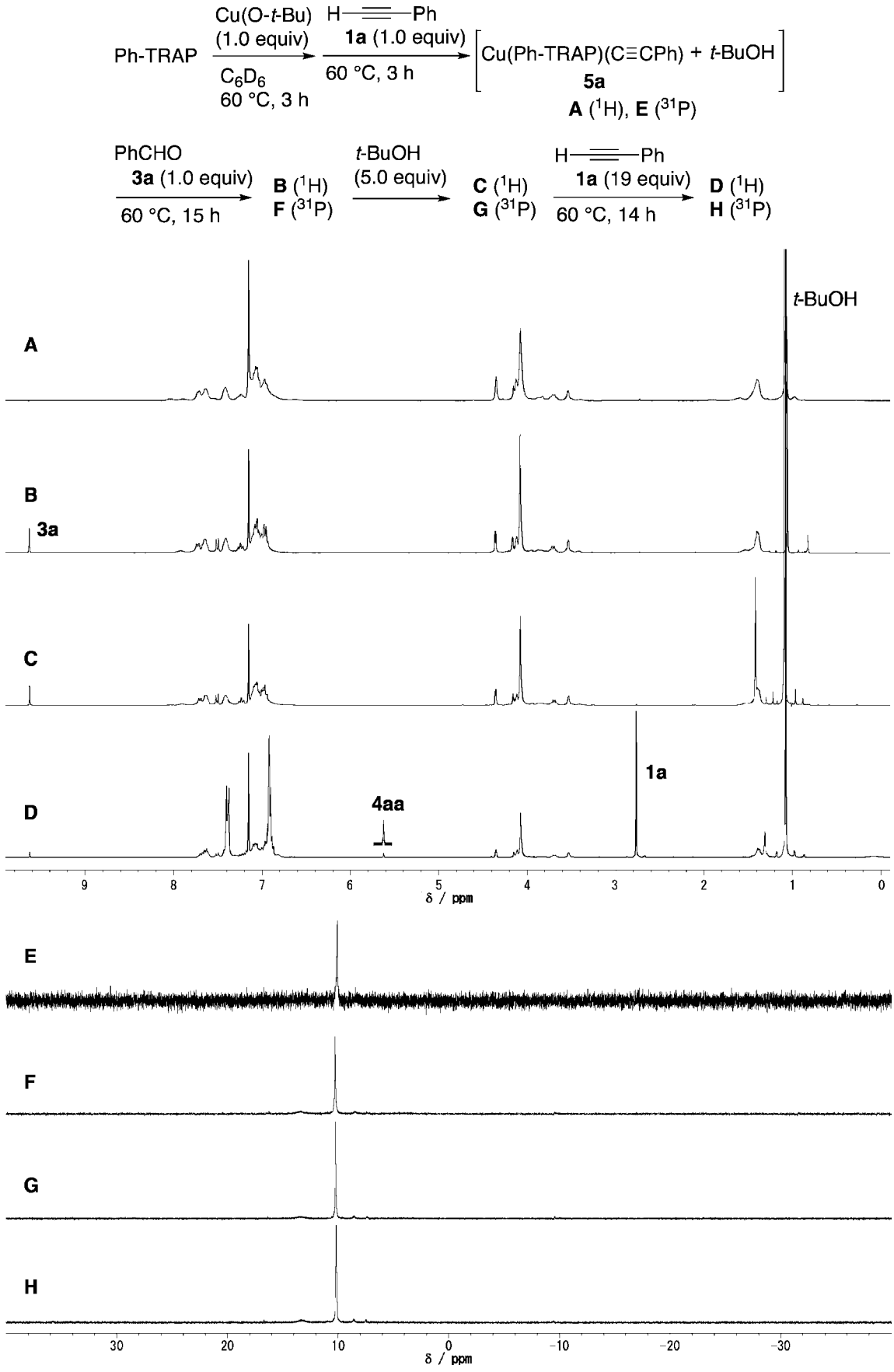


Figure 5. ^{1}H and ^{31}P NMR observation of the stoichiometric reaction of Ph-TRAP-Cu acetylide **5a** with PhCHO (**3a**) in C_6D_6.

hexane 1:99−20:80, detection: UV at 254 nm). High-resolution mass spectra were recorded on a JEOL JMS-FAB Mate mass spectrometer at the Center for Instrumental Analysis, Hokkaido University. Unless otherwise noted, materials were obtained from

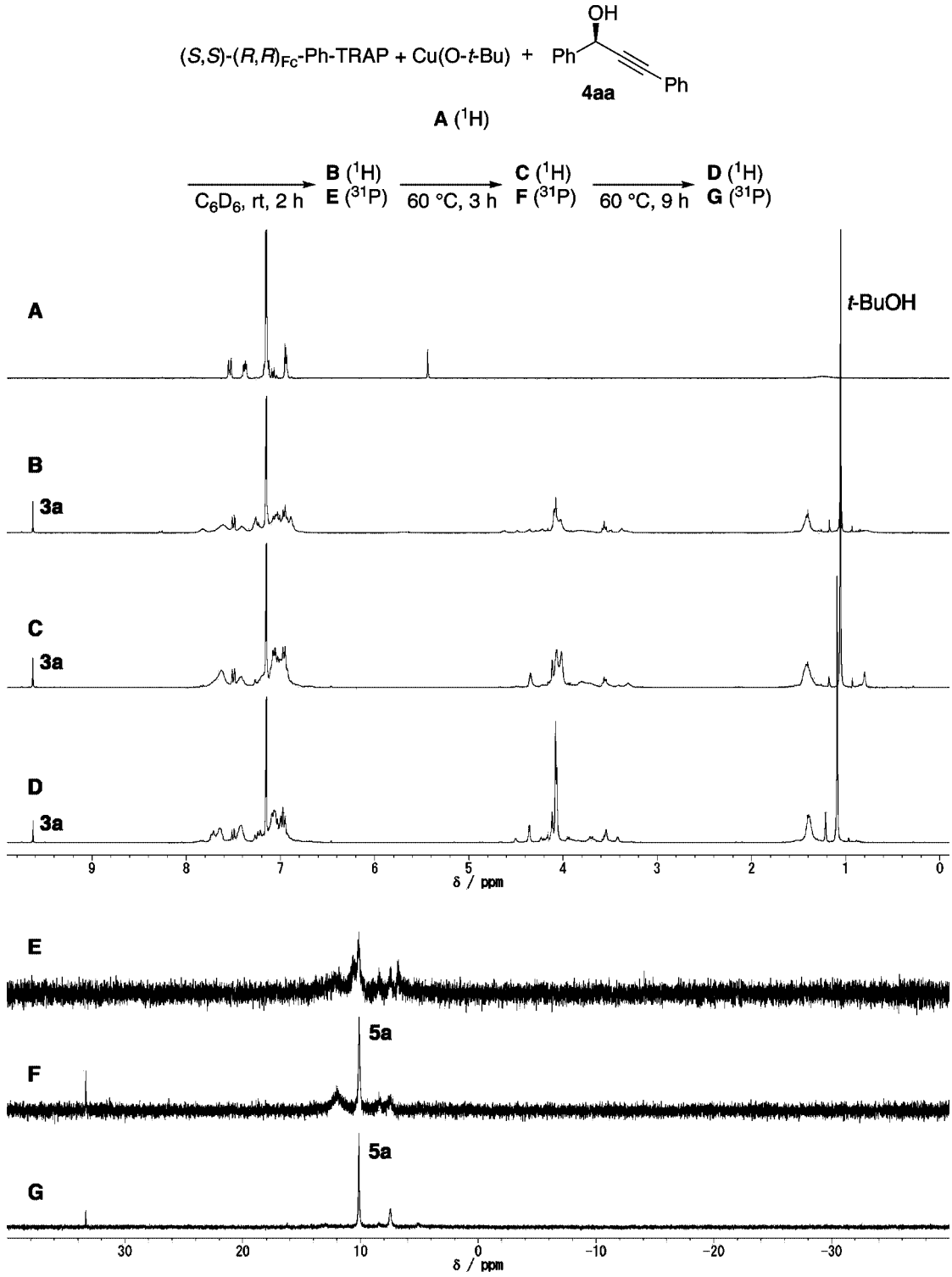


Figure 6. ^{1}H and ^{31}P NMR observation of the reaction of Ph-TRAP, Cu(O-*t*-Bu), and **4aa** (1:1:1) in C_6D_6.

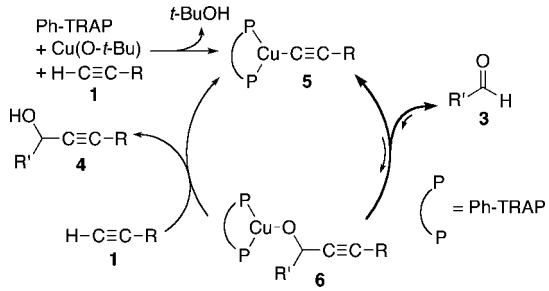
commercial suppliers and purified by standard procedures. All solvents for catalytic reactions were degassed via four freeze−pump−thaw cycles before use. Dry THF, CH_2Cl_2, and MeOH were purchased from Kanto Chem. Co., Inc., and used without further purification. Benzene and toluene were distilled from CaH_2. All other dry solvents were purchased from Kanto Chem. Co., Inc. Aldehydes and acetylenes were distilled before use. Cu(O-*t*-Bu) was prepared according to the reported procedure[28] and was sublimated before use. Xantphos,[14] DTBM-Xantphos,[15a] (*S*,*S*)-(*R*,*R*)-Ph-TRAP,[9a] (*R*,*R*)-(*S*,*S*)-Bu-TRAP,[9c] (*S*,*S*)-(*R*,*R*)- *p*-OMe-Ph-TRAP,[9a,b] and (*S*,*S*)-(*R*,*R*)-*p*-Cl-Ph-TRAP[9a,b] were prepared according to the reported procedures.

(*S*,*S*)-(*R*,*R*)$_{Fc}$-DTBM-TRAP. This compound was prepared following the procedure for the preparation of Ph-TRAP[9a] with slight modification as follows (procedures 1−4).

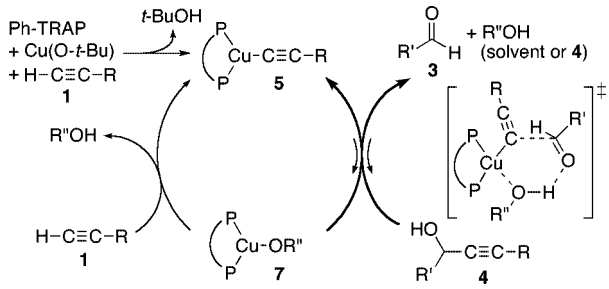
(1) Bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine Oxide. A two-necked 100 mL round-bottomed flask equipped with a reflux

(28) (a) Tsuda, T.; Hashimoto, T.; Saegusa, T. *J. Am. Chem. Soc.* **1972**, *94*, 658. See also: (b) Brussaard, Y.; Olbrich, F.; Behrens, U. *J. Organomet. Chem.* **1996**, *519*, 115.

Scheme 2. Possible Reaction Pathway for the Cu-Catalyzed Addition of Terminal Alkynes to Aldehydes (Pathway 1)



Scheme 3. Possible Reaction Pathway for the Cu-Catalyzed Addition of Terminal Alkynes to Aldehydes That Involves Direct Participation of an Alcoholic Solvent (Pathway 2)



condenser, a dropping funnel, and a magnetic stirring bar was charged with Mg turnings (1.625 g, 66.8 mmol), evacuated while being heated by a heat-gun for 10 min, and then back-filled with argon. Dry Et_2O (7.0 mL) was added through the dropping funnel. The dropping funnel was then charged with a solution of 1-bromo-3,5-di-*tert*-butyl-4-methoxybenzene[29] (DTBM-Br, 20.00 g, 66.8 mmol) in Et_2O (10 mL). Ten drops of the DTBM-Br solution was added, and the mixture was stirred until heat evolution and color change to black were observed. Then the rest of the DTBM-Br solution was added dropwise over 2.5 h. After the addition was complete, the dropping funnel was washed with Et_2O (2.5 mL). The mixture was then stirred at 40 °C overnight.

In a separate Schlenk tube, NaH (446 mg, 114 mmol, 60 wt %, mineral oil-coated) was washed three times with 5 mL of dry hexane·NaH and suspended in dry Et_2O (5.1 mL), and diethyl phosphite (1.75 mL, 13.6 mmol) was slowly added at rt. The mixture was diluted with 3.0 mL of dry Et_2O and then was transferred to the solution of the Grignard reagent via a cannula. The Schlenk tube was washed twice with 1.2 mL of dry Et_2O. The mixture was stirred at rt for 30 min and then at 50 °C for 20 h. After being cooled to rt and diluted with benzene (10 mL), the mixture was quenched with aqueous Na_2HPO_4 (5 mL). The mixture was filtered through a pad of Celite. The solid on the pad was well washed with benzene and EtOAc. A filtrate was shaken with saturated aqueous NaCl, and the resulting organic phase was separated. The aqueous phase was extracted with benzene and with EtOAc. The organic phases were combined and dried over $MgSO_4$. Solvents were removed *in vacuo* to give a yellow, viscous oil. Purification by silica gel chromatography (EtOAc/hexane 3:7) afforded 3.652 g (75%) of the title compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.402 (s, 36H, $-C(CH_3)_3$), 3.702 (s, 6H, $-OCH_3$), 7.543 (d, $^3J_{P-H}$ = 14.4 Hz, 4H, *Ar*), 8.032 (d, $^1J_{P-H}$ = 474.9 Hz, 1H, −P(O) *H*). ^{13}C NMR: δ (75.4 MHz, $CDCl_3$) δ 31.71 ($-C(CH_3)_3$), 35.87 ($-C(CH_3)_3$), 64.43 ($-OCH_3$), 125.17 (d, $^1J_{P-C}$ = 104.7 Hz, *ipso*(P)-Ar), 129.41 (d, $^2J_{P-C}$ = 13.1 Hz, *o*(P)-Ar), 144.75 (d, $^3J_{P-C}$ = 12.5 Hz, *m*(P)-Ar), 163.36 (d, $^4J_{P-C}$ = 2.9 Hz, *p*(P)-Ar). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 23.55. HRMS (ESI) (*m*/*z*): $[M + H]^+$ calcd for $C_{30}H_{48}O_3P$, 487.3341; found, 487.3336.

(29) Ochida, A.; Ito, H.; Sawamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 16486.

(2) $(R)_{Fc}$-2-[(*S*)-1-{Bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphinyl}ethyl]-1-iodoferrocene. $(R)_{Fc}$-2-[(*S*)-1-(*N*,*N*-Dimethylamino)ethyl]-1-iodoferrocene (91 wt % purity, 1.67 g, 3.97 mmol) was placed in a Schlenk tube. After the starting material was dissolved in dry CH_2Cl_2 (7.3 mL), iodomethane (1.4 mL, 22 mmol) was added. After the mixture was stirred at rt for 1 h, the solvent and excess iodomethane were evaporated.

Bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine oxide (4.04 g, 8.30 mmol) was placed in a separate Schlenk tube. The phosphine oxide was dissolved in dry THF (28 mL). A solution of BuLi in hexane (1.52 M, 5.6 mL, 8.5 mmol) was added dropwise for 10 min at 0 °C. The resulting solution was stirred at rt for 2 h, and then the solvent was removed under reduced pressure.

Under an argon atmosphere, the ammonium salt prepared above was dissolved in dry CH_3CN (44 mL). The solution was transferred into the Schlenk tube containing lithium bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphinite through a cannula, and then a reflux condenser was attached to the Schlenk tube. The mixture was stirred under reflux for 14 h. The mixture was cooled to rt. After water was added, the mixture was extracted twice with Et_2O. The combined organic phase was dried over $MgSO_4$, filtrated, and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 2:3). The fractions containing the desired compound were collected and evaporated to give the mixture of the title compound (2.95 mmol, 66% yield) and its deiodinated compound (ca. 2:1 molar ratio) as a dark orange solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.240 (s, 18H, $-C(CH_3)_3$), 1.484 (s, 18H, $-C(CH_3)_3$), 1.668 (dd, J = 15.1, 7.4 Hz, 3H, $-P(O)CH(CH_3)-$), 3.150 (pseudo-q, J = 7.4 Hz, 1H, $-P(O)CH(CH_3)-$), 3.616 (s, 3H, $-OCH_3$), 3.734 (s, 3H, $-OCH_3$), 4.157 (s, 5H, Cp), 4.293 (brs, 1H, Cp), 4.342 (brs, 1H, Cp), 4.522 (brs, 1H, Cp), 6.976 (d, J = 11.7 Hz, 2H, Ar), 7.788 (d, J = 11.4 Hz, 2H, Ar). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 15.73 ($-P(O)CHCH_3$), 31.61 ($-C(CH_3)_3$), 31.93 ($-C(CH_3)_3$), 34.91 (d, $^1J_{P-C}$ = 64.9 Hz, $-P(O)CHCH_3$), 35.60 ($-C(CH_3)_3$), 35.95 ($-C(CH_3)_3$), 47.45 (d, $^3J_{P-C}$ = 2.3 Hz, Cp), 64.47 ($-OCH_3$), 64.50 ($-OCH_3$), 66.43 (Cp), 68.49 (Cp), 71.31 (Cp), 73.30 (s, 5C, Cp), 123.42 (d, $^1J_{P-C}$ = 93.4 Hz, *ipso*(P)-Ar), 125.47 (d, $^1J_{P-C}$ = 97.9 Hz, *ipso*(P)-Ar), 130.24 (d, $^2J_{P-C}$ = 9.7 Hz, *o*(P)-Ar), 130.54 (d, $^2J_{P-C}$ = 11.4 Hz, *o*(P)-Ar), 142.73 (d, $^3J_{P-C}$ = 11.4 Hz, *m*(P)-Ar), 144.21 (d, $^3J_{P-C}$ = 11.4 Hz, *m*(P)-Ar), 162.79 (d, $^4J_{P-C}$ = 4.0 Hz, *p*(P)-Ar), 162.84 (d, $^4J_{P-C}$ = 3.4 Hz, *p*(P)-Ar). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 35.45. HRMS (ESI) (*m*/*z*): $[M + Na]^+$ calcd for $C_{42}H_{58}O_3NaPFeI$, 847.2415; found, 847.2338.

(3) $(R,R)_{Fc}$-2,2″-Bis[(*S*,*S*)-1-{bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphinyl}ethyl]-1,1″-biferrocene [(*S*,*S*)-(*R*,*R*)$_{Fc}$-DTBM-TRAP Oxide]. Copper powder (5.00 g, 78.7 mmol) and iodine (0.60 g, 2.36 mmol) were placed in a 50 mL Erlenmeyer flask. Distilled acetone (30 mL) was added, and the mixture was stirred until the dark brown supernatant turned colorless. Immediately, the copper powder was collected by filtration, washed sequentially with acetone (30 mL), acetone/concentrated aqueous HCl (1:1, 30 mL), and acetone (6 mL, 5 times), and then dried *in vacuo*. The activated copper powder (3.52 g, 55.4 mmol) was placed in a 200 mL round-bottomed flask containing $(R)_{Fc}$-2-[(*S*)-1-{bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphinyl}ethyl]-1-iodoferrocene (0.675 mmol). The organic material was dissolved in dry CH_2Cl_2 (10 mL). The solvent was evaporated, and the residue was dried under vacuum at 60 °C for 1 h. The flask was charged with argon and was capped with a glass stopper. The mixture was heated at 170 °C for 12 h and was allowed to cool to rt. The product was dissolved in CH_2Cl_2, and then the remaining copper powder was filtered through a Celite pad. The filtrate was concentrated, and the residue was passed through a short-path silica gel column with EtOAc and then was purified by gel permeation chromatography ($CHCl_3$) to give 347 mg (82%) of DTBM-TRAP oxide. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.351 (s, 36H, $-C(CH_3)_3$), 1.419 (s, 36H, $-C(CH_3)_3$), 1.783 (d,

J = 7.2 Hz, 3H, −P(O)CHCH_3), 1.783 (d, J = 7.5 Hz, 3H, −P(O)CHCH_3), 3.626 (s, 6H, −OCH_3), 3.710 (s, 6H, −OCH_3), 3.931 (brs, 4H, Cp and −P(O)CHCH$_3$), 4.249 (s, 12H, Cp), 4.321 (brs, 2H, Cp), 7.479 (d, J = 11.4 Hz, 4H, Ar), 7.605 (d, J = 11.1 Hz, 4H, Ar). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 20.07 (−P(O)CHCH$_3$), 31.79 (−C(CH$_3$)$_3$), 31.92 (−C(CH$_3$)$_3$), 32.53 (d, $^1J_{P-C}$ = 66.6 Hz, −P(O)CHCH), 35.63 (−C(CH$_3$)$_3$), 35.86 (−C(CH$_3$)$_3$), 64.44 (−OCH$_3$), 64.49 (−OCH$_3$), 65.76 (Cp), 67.46 (Cp), 69.14 (10C, Cp), 71.34 (Cp), 84.76 (d, J = 2.9 Hz, Cp), 87.86 (Cp), 124.09 (d, $^1J_{P-C}$ = 97.9 Hz, *ipso*(P)-Ar), 126.93 (d, $^1J_{P-C}$ = 96.2 Hz, *ipso*(P)-Ar), 130.40 (d, $^2J_{P-C}$ = 10.8 Hz, *o*(P)-Ar), 131.36 (d, $^2J_{P-C}$ = 9.7 Hz, *o*(P)-Ar), 143.68 (d, $^3J_{P-C}$ = 10.8 Hz, *m*(P)-Ar), 143.88 (d, $^3J_{P-C}$ = 11.4 Hz, *m*(P)-Ar), 162.65 (d, $^4J_{P-C}$ = 2.9 Hz, *p*(P)-Ar), 162.80 (d, $^4J_{P-C}$ = 3.4 Hz, *p*(P)-Ar). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 37.00. HRMS (ESI) (*m*/*z*): [M + Na]$^+$ calcd for $C_{84}H_{116}O_6NaP_2Fe_2$, 1417.6844; found, 1417.6851.

(4) (R,R)$_{Fc}$-2,2″-Bis[(S,S)-1-{bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino}ethyl]-1,1″-biferrocene [(S,S)-(R,R)$_{Fc}$-DTBM-TRAP]. The reduction method developed by Spencer et al. was followed.[30] Thus, (S,S)-(R,R)$_{Fc}$-DTBM-TRAP oxide (1.60 g, 1.12 mmol) and PPh_3 (1.17 g, 4.46 mmol) were placed in a Schlenk tube. Toluene (17 mL), THF (17 mL), and $HSiCl_3$ (4.5 mL, 44.5 mmol) were successively added. A reflux condenser was attached to the Schlenk tube, and the mixture was heated at 80 °C for 44 h. After being cooled to rt, the reaction mixture was quenched by argon-saturated water, and then benzene and 20% aqueous NaOH were added successively. The mixture was moved to a separation funnel, an organic phase was separated, and an aqueous phase was extracted with benzene. The combined organic phase was dried over Na_2SO_4, filtered, and concentrated using a rotary evaporator. The residue was quickly passed through a short-pass silica gel column (benzene) to give 1.16 g (76%) of (S,S)-(R,R)$_{Fc}$-DTBM-TRAP as an orange powder. $[\alpha]^{21}{}_D$ +142.1 (*c* 0.50, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6): δ 1.339 (s, 36H, −C(C H_3)$_3$), 1.474 (s, 36H, −C(CH_3)$_3$), 1.606 (brs, 6H, −P(O)CHCH_3), 3.2−3.4 (br, 2H, −P(O)CHCH_3), 3.478 (s, 6H, −OCH_3), 3.500 (s, 6H, −OCH_3), 3.95−4.15 (br, 4H, Cp), 4.197 (10H, Cp), 4.632 (brs, 2H, Cp), 7.424 (brs, 4H, Ar), 7.713 (brs, 4H, Ar). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 13.96 (−PCH CH$_3$), 20.31 (−PCHCH$_3$), 32.24 (−C(CH$_3$)$_3$), 32.35 (−C(CH$_3$)$_3$), 35.74 (−C(CH$_3$)$_3$), 35.88 (−C(CH$_3$)$_3$), 63.96 (−OCH$_3$), 64.01 (−OCH$_3$), 66.07 (Cp), 68.07 (Cp), 69.66 (Cp), 70.00 (10C, Cp), 85.00 (Cp), 91.48 (br, Cp), 129.79 (br, Ar), 133.19 (Ar), 135.33 (br, Ar), 142.45 (*o*(P)-Ar), 143.17 (*o*(P)-Ar), 158.70 (*p*(P)-Ar), 160.35 (*p*(P)-Ar). ^{31}P NMR (121.4 MHz, C_6D_6): δ −1.46. HRMS (ESI) (*m*/*z*): [M + H]$^+$ calcd for $C_{84}H_{117}O_4NaP_2Fe_2$, 1363.7126; found, 1363.7102.

(S,S)$_{Fc}$-(R,R)-Terph-TRAP. This compound was prepared following the procedure for the preparation of Ph-TRAP[9a] with slight modification as follows (procedures 1−4).

(1) Bis(3,5-diphenylphenyl)phosphine Oxide. A two-necked, 100 mL, round-bottomed flask equipped with a reflux condenser, a dropping funnel, and a magnetic stirring bar was charged with Mg turnings (1.022 g, 42 mmol), evacuated while being heated by a heat-gun for 10 min, and then back-filled with argon. Dry THF (6.5 mL) was added through the dropping funnel. The dropping funnel was then charged with a solution of 1-bromo-3,5-diphenylbenzene[31] (13.00 g, 13.56 mmol) in THF (35 mL). Ten drops of the DTBM-Br solution was added, and the mixture was stirred until heat evolution and color change to black were observed. Then the rest of the DTBM-Br solution was added dropwise over 5 h. After the addition was complete, the dropping funnel was washed with THF (5 mL). The mixture was then stirred at 50 °C for 1 h. N,N,N',N'-tetramethylethylenediamine (7.2 mL, 48mmol) and (EtO)$_2$P(O)H (1.75 mL, 13.56 mmol) were added to the mixture at rt. The mixture was stirred at 50 °C for 13 h and was cooled to 0 °C. Water was carefully added. EtOAc was then added, and the mixture was stirred vigorously until clear phase separation occurred. An organic phase was separated. An aqueous phase was extracted with EtOAc. The combined organic phase was dried over $MgSO_4$, filtrated, and concentrated to give a pale yellow oil. The oil was purified with silica gel chromatography (EtOAc/hexane 3:7) followed by gel permeation chromatography ($CHCl_3$) to give 3.652 g (53%) of the title compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30−7.60 (m, 12H), 7.60−7.75 (m, 8.5H), 9.105 (s, 0.5H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 128.08 (s), 128.28 (d, J = 125.8 Hz, *ipso*(P)-Ar), 128.24 (s), 130.52 (d, J = 2.8 Hz, *m*(P)-Ar), 132.04(s), 133.38 (s), 139.89 (s, *p*(P)-Ar), 142.87 (d, J = 12.3 Hz, *o*(P)-Ar). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 22.7. HRMS (ESI) (*m*/*z*): [M]$^+$ calcd for $C_{36}H_{27}OP$, 506.1779; found, 506.1802.

(2) (R)$_{Fc}$-2-[(S)-1-{Bis(3,5-diphenylphenyl)phosphinyl}ethyl]-1-iodoferrocene. (R)$_{Fc}$-2-[(S)-1-(N,N-Dimethylamino)ethyl]-1-iodoferrocene (91 wt % purity, 1.29 g, 3.07 mmol) was placed in a Schlenk tube. After the starting material was dissolved in dry CH_2Cl_2 (5.19 mL), iodomethane (956 μL, 15.4 mmol) was added. After the mixture was stirred at rt for 1 h, the solvent and excess iodomethane were evaporated.

Bis(3,5-diphenylphenyl)phosphine oxide (3.11 g, 6.14 mmol) was placed in a separate Schlenk tube. The phosphine oxide was dissolved in dry THF (45.2 mL). A solution of BuLi in hexane (1.58 M, 4.0 mL, 6.35 mmol) was added dropwise for 10 min at 0 °C. The resulting solution was stirred at rt for 2 h, and then the solvent was removed under reduced pressure.

Under an argon atmosphere, the ammonium salt prepared above was dissolved in dry CH_3CN (31 mL). The solution was transferred into the Schlenk tube containing lithium bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphinite through a cannula, and then a reflux condenser was attached to the Schlenk tube. The mixture was stirred under reflux for 5 h. The mixture was cooled to rt. After water was added, the mixture was extracted twice with Et_2O. The combined organic phase was dried over $MgSO_4$, filtrated, and then concentrated. The residue was purified by silica gel chromatography (EtOAc/hexane 3:7). The fractions containing the desired compound were collected and evaporated to give the mixture of the title compound (2.19 mmol, 57% yield) and its deiodinated compound (ca. 5:1 molar ratio) as a dark orange solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.798 (dd, J = 15.3, 7.2 Hz, 3H, −P(O)CHCH_3), 3.457 (m, 1H, −P(O)CHCH$_3$), 4.165 (s, 5H, Cp), 4.242 (t, J = 1.1 Hz, 1H, Cp), 4.359 (brs, 1H, Cp), 4.638 (brd, J = 0.9 Hz, 1H, Cp), 7.30−7.62 (m, 20H), 7.727 (d, J = 8.0 Hz, 4H), 8.194 (d, J = 11.0 Hz, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 15.91 (d, $^2J_{P-C}$ = 1.7 Hz, −P(O)CHCH$_3$), 34.51 (d, $^1J_{P-C}$ = 65.5 Hz, −P(O)CHCH$_3$), 46.69 (d, J = 2.9 Hz, *Cp*), 66.80 (d, J = 1.7 Hz, Cp), 68.54 (s, Cp), 68.95 (s, Cp), 71.40 (s, 5C, Cp), 89.05 (d, J = 1.2 Hz, Cp), 127.69 (s), 128.02 (d, $^1J_{P-C}$ = 114.5 Hz, *ipso*(P)-Ar), 128.09 (s), 128.26 (d, $^1J_{P-C}$ = 119.7 Hz, *ipso*(P)-Ar), 129.14 (s), 129.26 (s), 129.56 (s), 129.69 (s), 131.16 (s), 131.89 (s), 132.37 (s), 133.18 (s), 140.16 (s), 140.39 (s), 141.27 (d, $^2J_{P-C}$ = 12.0 Hz, *ortho*(P)-Ar), 142.46 (d, $^2J_{P-C}$ = 11.4 Hz, *ortho*(P)-Ar). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 34.24. HRMS (ESI) (*m*/*z*): [M]$^+$calcd for $C_{48}H_{38}OPFeI$, 867.0952; found, 867.0943.

(3) (R,R)$_{Fc}$-2,2″-Bis[(S,S)-1-{bis(3,5-diphenylphenyl)phosphinyl}ethyl]-1,1″-biferrocene [(S,S)-(R,R)$_{Fc}$-Terph-TRAP Oxide]. The activated copper powder (4.02 g, 63.3 mmol) was placed in a 200 mL round-bottomed flask containing (R)$_{Fc}$-2-[(S)-1-{bis(3,5-diphenylphenyl)phosphinyl}ethyl]-1-iodoferrocene (0.772 mmol). The organic material was dissolved in dry CH_2Cl_2 (10 mL). The solvent was evaporated, and the residue was dried under vacuum at 60 °C for 1.5 h. The flask was charged with argon and was capped with a glass stopper. The mixture was heated at 170 °C for 13 h and was allowed to cool to rt. The product was dissolved in CH_2Cl_2, and then the remaining copper powder was filtered through a Celite

(30) Wu, H.-C.; Yu, J.-Q.; Spencer, J. B. *Org. Lett.* **2004**, *6*, 4675.

(31) Matsumoto, K.; Hatano, K.; Umezawa, N.; Higuchi, T. *Synthesis* **2004**, *13*, 2181.

pad. The filtrate was concentrated, and the residue was passed through a short-pass silica gel column with EtOAc/hexane (1:9) and then purified by gel permeation chromatography ($CHCl_3$) to give 206 mg (37%) of Terph-TRAP oxide. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.75−1.90 (brd, 6H, −P(O)CHCH_3), 4.108 (brt, 2H, −P(O)CHCH$_3$), 4.361 (brs, 10H, Cp), 4.0−4.6 (br, 6H, Cp), 7.10−7.35 (m, 20H), 7.4−7.5 (br, 2H), 7.58 (d, J = 6.6 Hz, 8H), 7.83 (brd, 4H), 7.90 (brs, 4H), 8.13 (d, J = 10.7 Hz, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 18.5−20.0 (br, −P(O)CH CH$_3$), 31.6 (brd, J = 67.6 Hz, P(O)CHCH$_3$), 65.6 (br, Cp), 68.5 (s, Cp), 69.4 (s, 10C, Cp), 84.6 (br, Cp), 127.5 (s), 127.8 (s), 127.8 (d, $^1J_{P-C}$ = 109.9 Hz, *ipso*(P)-Ar), 128.0 (d, $^1J_{P-C}$ = 119.1 Hz, *ipso*(P)-Ar), 129.1 (s), 129.2 (s), 129.6 (s), 129.7 (s), 133−134 (br), 134−136 (br), 139.8 (s), 140.1 (s), 141.2 (d, $^2J_{P-C}$ = 12.5 Hz, *ortho*(P)-Ar), 141.6 (d, $^2J_{P-C}$ = 10.9 Hz, *ortho*(P)-Ar). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 35.3. HRMS (ESI) (*m*/*z*): $[M + Na]^+$ calcd for $C_{96}H_{76}O_2P_2Fe_2Na$, 1457.3917; found, 1457.3905.

(4) (R,R)$_{Fc}$-2,2″-Bis[(S,S)-1-{bis(3,5-diphenylphenyl)phosphino}ethyl]-1,1″-biferrocene [(S,S)-(R,R)$_{Fc}$-Terph-TRAP]. The reduction method developed by Spencer et al. was followed.[30] Thus, (S,S)-(R,R)$_{Fc}$-Terph-TRAP oxide (100.0 mg, 0.0697 mmol) and PPh_3 (73.1 mg, 0.279 mmol) were placed in a Schlenk tube. Toluene (1 mL), THF (1 mL), and $HSiCl_3$ (282 μL, 2.79 mmol) were successively added. A reflux condenser was attached to the Schlenk tube, and the mixture was heated at 80 °C for 13.5 h. After being cooled to rt, the reaction mixture was quenched by argon-saturated water, and then benzene and 20% aqueous NaOH were added successively. The mixture was moved to a separation funnel. An organic phase was separated, and an aqueous phase was extracted with benzene. The combined organic phase was washed with saturated aqueous $NaHCO_3$, brine, and water, dried over Na_2SO_4, filtered, and concentrated using a rotary evaporator. The ^{1}H NMR analysis indicated that the reduction was not complete and that the crude material contained the desired compound, partly reduced compound (phosphinephosphine oxide), and the starting compound. Purification of the crude material by silica gel chromatography (EtOAc/hexane 1:99, and then benzene) to give 45.1 mg (46%) of (S,S)$_{Fc}$-(R,R)$_{Fc}$-Terph-TRAP as an orange powder. $[\alpha]^{21}_D$ +341.8 (c 0.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.524 (d, J = 7.2 Hz, 6H, −P(O)CHCH_3), 3.778 (br, 2H, −P(O)CHCH$_3$), 3.930 (brs, 2H), 4.075 (s, 10H, Cp), 4.243 (brs, 2H, Cp), 4.535 (brs, 2H, Cp), 6.92−7.05 (m, 12H), 7.10−7.20 (m, 4H), 7.235 (t, J = 7.4 Hz, 8H), 7.370 (dd, J = 7.2, 1.8 Hz, 8H), 7.53−7.63 (m, 10H), 7.781 (brs, 2H), 7.931 (brs, 4H), 8.026 (brs, 4H). ^{13}C NMR (75.4 MHz, C_6D_6): δ 13.7 (−P(O)CH CH$_3$), 33.1 (br, −P(O) CHCH$_3$), 66.2 (br, Cp), 68.1 (s, Cp), 70.0 (s, 10C, Cp), 70.7 (br, Cp), 85.5 (br, Cp), 92.0 (t, J = 1.9 Hz, Cp), 125.5 (s), 126.4 (s), 127.2 (s), 127.3 (s), 127.6 (s), 128.5 (s), 128.8 (s), 129.1 (s), 131.4 (pseudo t), 131.8 (pseudo t). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 1.04. HRMS (ESI) (*m*/*z*): $[M + H]^+$ calcd for $C_{96}H_{77}P_2Fe_2$, 1403.4199; found, 1403.4198.

General Procedure for the Cu(I)-Catalyzed Addition of 1 to 3 (Tables 6 and 7). In a glovebox, Cu(O-*t*-Bu) (22 μmol, 3.0 mg) and a ligand (22 μmol) were placed in a screw-capped test tube and were dissolved in anhydrous, degassed *t*-BuOH (0.44 mL). After being sealed with a septum cap, the test tube was removed from the glovebox. An aldehyde (**3**, 0.22 mmol) and an alkyne (**1**, 48.2 μL, 0.44 mmol) were added, and then the septum cap was quickly replaced with a screw cap. The mixture was heated at 40 °C for 24 h, then was cooled to rt. The mixture was diluted with $CDCl_3$, and 1,1,2,2-tetrachloroethane (11.6 μL, 0.11 mmol) was added as an internal standard. The resulting solution was subjected to ^{1}H NMR spectroscopy for the analysis of yield of **4**. The evaporated crude material was subjected to column chromatography on silica gel (EtOAc/hexane) to obtain pure **4**. The enantiomeric excess of **4** was determined by HPLC.

Characterization of Propargylic Alcohols (4). Characterization of new compounds (**4ca**, **4ag**, **4ai**, **4aj**, **4al**) and known compounds **4ba** and **4ad** has been reported in ref 11 as Supporting Information.

Acknowledgment. This work was supported by Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from the Ministry of Education, Culture, Sports, Science and Technology. Y.A. was supported by MEXT programs, Initiatives for Attractive Education in Graduate Schools (T-type Chemists with Lofty Ambition), and GCOE (Catalysis as the Basis for Innovation in Materials Science).

Supporting Information Available: Details of the ^{31}P NMR experiments for the complexation of Xantphos and *i*-Pr-Duphos with copper(I) species. NMR tables for DTBM-TRAP, Terph-TRAP, and the intermediates in the synthesis of these compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OM800667C