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Enantioselective Addition of Terminal Alkynes to Aldehydes Catalyzed by a Cu(I)–TRAP Complex

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

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

sawamura@sci.hokudai.ac.jp

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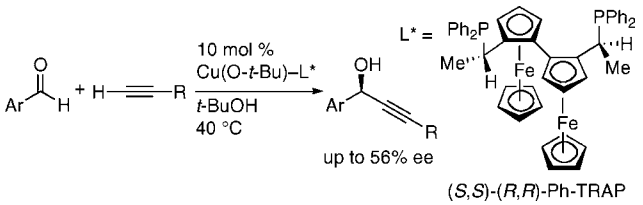
ABSTRACT



The addition of terminal alkynes to aromatic aldehydes was carried out 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. Furthermore, according to stoichiometric reactions, the reaction presumably involves the addition of a TRAP-coordinated Cu(I) acetylide to an aldehyde.

The addition of terminal alkynes to aldehydes serves as an important carbon−carbon bond formation reaction in the synthesis of complex molecules.[1] 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] reactions that feature the catalysis of Cu, to the best of our knowledge, have yet to be reported. 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. Furthermore, this is the first application of TRAP to Cu catalysis.

Recently, we have reported on the significant rate-accelerating effects of Xantphos ligands[11] in the Cu(I)-catalyzed dehydrogenative silylation of alcohols[12] and in the

(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) (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.

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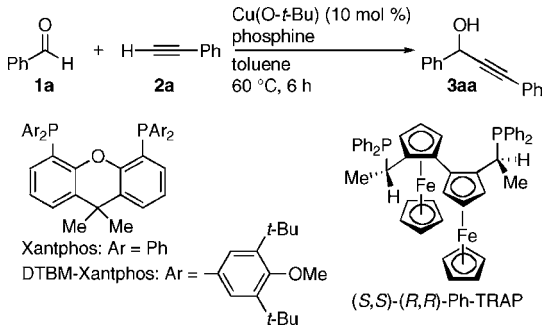
reaction of a diboron and allylic carbonates to produce allylboron compounds.[13] The high catalytic activities are attributable to the large P−Cu−P bite angle that induces large distributions of active monomeric Cu species, such as (Xantphos)Cu−X [X = OR, H, B(OR)$_2$], in the aggregation equilibriums. 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.

A series of Cu(I)−phosphine catalysts were prepared in situ by mixing Cu(O-*t*-Bu) with phosphines (Table 1).

Table 1. Ligand Effect in the Cu-Catalyzed Addition of **2a** to **1a**[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	DBFphos	2
9	Xantphos	10
10	DTBM-Xantphos	20
11	(*S*,*S*)-(*R*,*R*)-Ph-TRAP	77 (27% ee, *R*)

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

Catalytic activities of the resulting Cu(I) complexes (10 mol %) were evaluated by the yields of propargylic alcohol **3aa** via reaction of benzaldehyde (**1a**) and phenylacetylene (**2a**, 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 (entry 9).[14] Reactions that involved DPEphos[12a] and DBFphos,[12a,15] which are structurally related to Xantphos, showed traces of conversion (entries 7 and 8, respectively). Because higher yield of **3aa** was obtained by introducing a bulky substituent in the *P*-phenyl groups of Xantphos (entry 10),[16] we can assume that the steric congestion around the metal center exerts an additional effect to the deaggregation of the Cu acetylide. Accordingly, the use of TRAP chiral bisphosphine, which feature an extraordinarily large bite angle, resulted in a significantly higher yield of **3aa** (77%, entry 11). Furthermore, the enantiomeric excess of the product indicated that the chirality of the (*S*,*S*)-(*R*,*R*)-TRAP ligand can exert some influence on the enantioselectivity of the addition reaction.

It should be noted that only DTBM-Xantphos and Ph-TRAP gave homogeneous, yellow solution under the reaction conditions (Table 1, entries 10 and 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 only the TRAP ligand exhibited significant catalyst-activating effect and enantioselectivity (Figure 1),

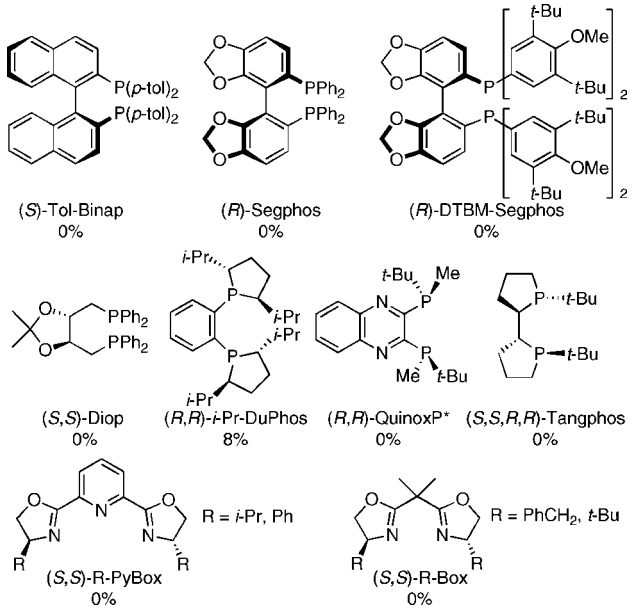


Figure 1. Chiral ligands and yields of **3aa** (**1a**/**2a**/Cu(O-*t*-Bu)/ligand = 1:2:0.1:0.1, toluene, 60 °C, 6 h).

thus confirming the importance of having a large bite angle for the effectiveness of the Cu catalysts.

To optimize the Cu−TRAP catalytic system, the conversion to **3aa** was carried out using various reaction solvents

(12) (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.

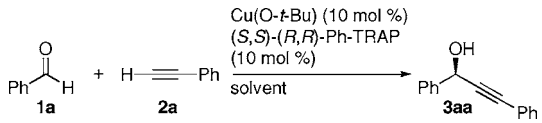
(13) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034.

(14) The reaction in the presence of K(O-*t*-Bu) (10 mol %) consumed the aldehyde (**1a**, 4% recovery) but gave no addition product **3aa**. 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.

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

(16) For the synthesis and use of DTBM-Xantphos, see ref 12a.

Table 2. Solvent Effect in the Enantioselective Cu-Catalyzed Addition of **2a** to **1a**[a]



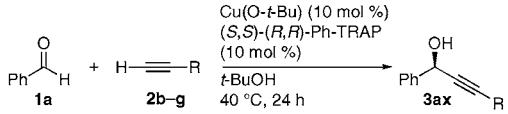
entry	solvent	T (°C)	time (h)	isolated yield[b] (%)	ee (%)
1	toluene	60	6	74	27
2	benzene	60	6	69	23
3	CH_2Cl_2	60	6	0	N.A.
4	THF	60	6	50	33
5	DMI	60	6	24	31
6	MeOH	60	6	91	25
7	EtOH	60	6	83	29
8	*i*-PrOH	60	6	87	30
9	$(i\text{-Pr})_2$CHOH	60	6	81	35
10	*t*-BuOH	60	6	91	42
11[c]	*t*-BuOH	40	24	87	51

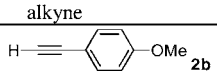
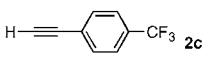
[a] **1a** (0.24−0.62 mmol, 1 M)/**2a**/Cu(O-*t*-Bu)/Ph−TRAP = 1:2:0.1:0.1. [b] Unreacted **1a** and **2a** were quantitatively recovered. [c] [**1a**] = 0.5 M.

(60 °C, 6 h). As shown in Table 2 (entries 1−10), alcohols were more effective as solvents; furthermore, higher enantiomeric excesses of **3aa** corresponded to larger alcohols (entries 6−10). Based on entry 10, which afforded (*R*)-**3aa** with 42% ee in 91% yield, the optimal solvent was identified as *t*-BuOH. Additionally, the use of *t*-BuOH allowed a lower reaction temperature (40 °C) that afforded **3aa** with a higher enantiomeric excess (51% ee, entry 11).

The influence of various alkyne substrates on the reactivity and enantioselectivity were examined using the reaction with **1a** under constant conditions (10 mol % Cu−TRAP, 40 °C, 24 h, Table 3). Whereas the electron-donating *p*-MeO

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



entry	alkyne	isolated yield[b] (%)	ee (%)
1	 **2b**	92[c]	48
2	 **2c**	37	45
3	H−≡−Bu **2d**	83	41
4	H−≡−*i*-Pr **2e**	32	43
5	H−≡−*t*-Bu **2f**	7	N.D.
6	H−≡−$SiMe_3$ **2g**	8[c]	36

[a] **1a** (0.20−0.22 mmol, 0.5 M)/**2**/Cu(O-*t*-Bu)/Ph−TRAP = 1:2:0.1:0.1. [b] Unreacted aldehyde **1a** and alkyne **2** were quantitatively recovered unless otherwise noted. [c] Recovery of alkyne was not quantitative.

substituent on the aromatic ring of phenylacetylene (entry 1) did not affect the yield or the enantiomeric excess, the electron-withdrawing *p*-CF_3 (entry 2) substituent resulted in a substantial drop in the yield. For the reactions of aliphatic alkynes **2d**−**f**, our catalytic system was also found to be 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 (**2g**, entry 6).

Next, the effect of various aldehydes on the reactivity and enantioselectivity were examined using the reaction with **2a** (10 mol % of Cu−TRAP, 40 °C, 24 h, Table 4). As shown in entries 1−3, 6, and 8, 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 7, 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 (entry 9) showed activating effects with slightly negative effect on the selectivity, whereas a bulky phenyl group in the same position caused overcrowded conditions (entry 10). Similar steric effects were also observed between the isomeric naphthaldehydes (entries 12, 13). In the cases of aliphatic aldehydes such as **1o** and **1p**, the Cu−TRAP catalyst did not exhibit any activity (entries 14 and 15).

To gain insight into the mechanism of the Cu−TRAP catalysis, stoichiometric reactions were carried out. 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. Upon addition of **2a** (1 equiv), the yellow color intensified, while the ^{31}P NMR signals converged into a major singlet (δ 10.1) accompanied by two minor broad signals (δ 8.51 and 13.1). Based on the similarity to that of $[CuC{\equiv}CPh]_n$ and Ph-TRAP (Cu/TRAP = 1:1, 60 °C, 3 h), the major signal was assigned to the TRAP-coordinated Cu(I) acetylide species [Cu(η^1-C≡CPh)(Ph-TRAP)] (**A**) (see the Supporting Information).

To investigate the reactivity of acetylide **A**, a solution containing **A** and *t*-BuOH, which was released from Cu(O-*t*-Bu), was treated with **1a** (1 equiv) and heated at 60 °C for 15 h. According to the ^{1}H NMR spectrum, both complex **A** and **1a** were intact. Furthermore, changes in the spectrum were not observed even upon treatment of 5 equiv of *t*-BuOH (as a possible proton source) and heating at 60 °C for an

Scheme 1. Proposed Mechanism for Cu−TRAP-Catalyzed Alkynylation of Aldehydes

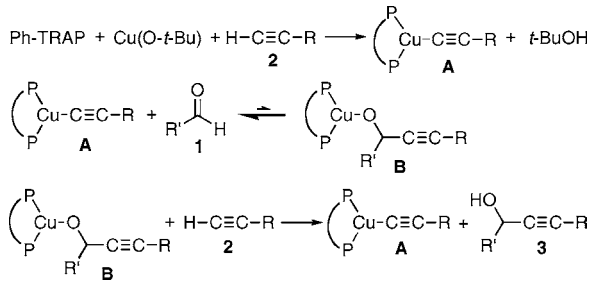
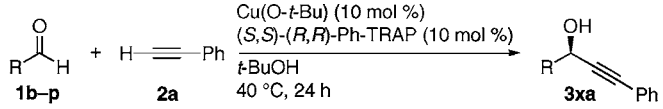
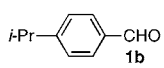
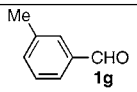
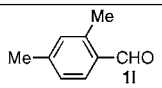
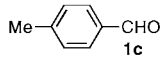
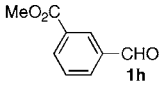
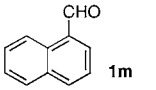
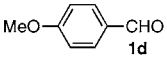
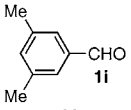
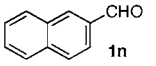
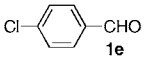
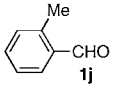
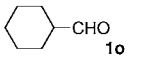
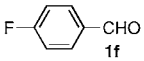
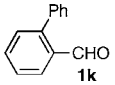
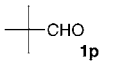


Table 4. Enantioselective Cu-Catalyzed Addition of **2a** to Various Aldehydes[a]



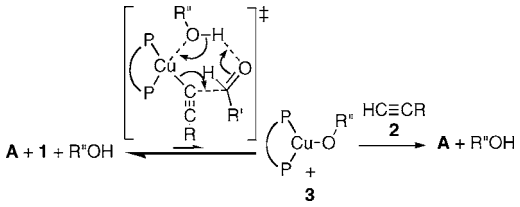
entry	aldehyde	yield[b]	ee	entry	aldehyde	yield[b]	ee	entry	aldehyde	yield[b]	ee
1	 **1b**	48%	55% ee	6	 **1g**	73%	52% ee	11	 **1l**	53%	47% ee
2	 **1c**	38%	54% ee	7	 **1h**	99%	48% ee	12	 **1m**	82%	54% ee
3	 **1d**	18%	56% ee	8	 **1i**	55%	56% ee	13	 **1n**	8%	54% ee
4	 **1e**	93%	43% ee	9	 **1j**	92%	45% ee	14	 **1o**	0%	N.A.
5	 **1f**	92%	51% ee	10	 **1k**	63%	39% ee	15	 **1p**	0%	N.A.

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

additional 3 h (except for the increased *t*-BuOH signals). Addition product **3aa** was produced when the mixture was treated with 19 equiv of **2a** (56% conversion, 60 °C, 14 h).

On the basis of these results, a possible reaction mechanism (Scheme 1) can be described as follows: first, (propargyl alcoholato) Cu(I) (**B**) is formed from acetylide **A** and aldehyde **1** through a reversible process with a strong preference toward the starting materials. Next, propargylic alcohol **3** is formed through metathesis between Cu(I) alkoxide **B** and alkyne **2**, which is irreversibly driven by the stability of Cu(I) acetylide **A**.

Scheme 2. Possible Participation of Alcohol



As mentioned above, our studies have revealed that the use of alcohols can accelerate the reaction, and bulkier alcohols can increase the enatioselectivity. Such solvent effects imply that the alcohols can directly participate in the C−C bond formation, as shown in Scheme 2.

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 show that the TRAP ligand is crucial for the Cu catalytic system. Insight into the reaction mechanism was gained via stoichiometric reactions and may help in the design of more advanced catalysts.

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Supporting Information Available: Experimental procedures and NMR spectra for stoichiometric reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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