ORGANIC LETTERS

2007
Vol. 9, No. 16
2997−3000

Copper(I) Alkoxide-Catalyzed Alkynylation of Trifluoromethyl Ketones

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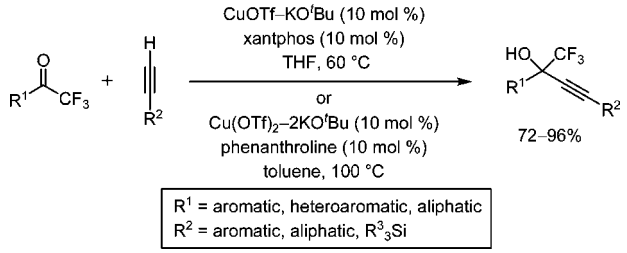
Received April 30, 2007

ABSTRACT



A general method for direct alkynylation of trifluoromethyl ketones was developed by using CuO^{t}Bu–xantphos or phenanthroline complexes as catalysts. The ligands significantly enhanced the catalyst activity. In addition, KOTf, generated in the catalyst preparation step, exhibited some acceleration effects. A preliminary extension to a catalytic enantioselective CF_3-substituted tertiary propargyl alcohol synthesis (up to 52% ee) is also described.

The development of new methods for catalytic enantioselective tetrasubstituted carbon-constructing C−C bond-formation with ketones and ketoimines is highly challenging.[1] To overcome the moderate reactivity of these substrates, organometallic reagents or metal enolates are generally used as nucleophiles. By contrast, reactions involving in situ generation of reactive nucleophiles (such as enolates, enamines, or metal alkynides) from stable, purely organic molecules (such as ketones, aldehydes, or alkynes) via asymmetric catalyst-mediated deprotonation are more advantageous in terms of atom economy.[2] Although such direct catalytic asymmetric reactions have been intensively studied by using aldehydes and aldimines as substrates,[3] extension to direct catalytic asymmetric tetrasubstituted carbon synthesis is still immature.[4,5] In this Letter, we describe a direct catalytic alkynylation of trifluoromethyl ketones with broad substrate generality. The methodology can be a platform for a direct catalytic enantioselective CF_3-substituted tertiary propargyl alcohol synthesis.[6−8]

(1) (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (b) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873−888.

(2) Trost, B. M. *Science* **1991**, *254*, 1471−1477.

(3) Catalytic asymmetric hydrocyanation, Michael reaction, nitro-aldol reaction, nitro-Mannich reaction, direct aldol reaction, direct Mannich reaction, and alkynylation are in this categorey. For a general review of asymmetric catalysis, see: *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999.

(4) HCN is the only nucleophile that can be applied to direct catalytic enantioselective tetrasubstituted carbon synthesis with unactivated ketones and ketoimines: (a) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867−890. (b) Charavot, M.; Byrne, J. J.; Chavant, Y.; Vallée, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1147−1150. (c) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3153. (d) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964−8965.

(5) Except for hydrocyanation, α-keto (or imino) carbonyl compounds (or α-keto phosphonates) are the only substrates used in direct catalytic asymmetric tetrasubstituted carbon synthesis (nitro-aldol reactions for 5a−e; direct aldol reactions for 5f−i; alkynylation for 5j): (a) Christensen, C.; Juhl, K.; Jørgensen, K. A. *Chem. Commun.* **2001**, 2222−2223. (b) Christensen, C.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875−4881. (c) Lu, S.-F.; Du, D.-M.; Zhang, S.-W.; Xu, J. *Tetrahedron: Asymmetry* **2004**, *15*, 3433−3441. (d) Du, D.-M.; Lu, S.-F.; Fang, T.; Xu, J. *J. Org. Chem.* **2005**, *70*, 3712−3715. (e) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732−733. (f) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476−4478. (g) Tokuda, O.; Kano, T.; Gao, W.-G.; Ikemoto, T.; Maruoka, K. *Org. Lett.* **2005**, *7*, 5103−5105. (h) Tang, Z.; Cun, L.-F.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2006**, *8*, 1263−1266. (i) Samata, S.; Zhao, C.-G. *J. Am. Chem. Soc.* **2006**, *128*, 7442−7443. (j) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451−3453.

10.1021/ol071003k CCC: $37.00
Published on Web 07/13/2007

Recently, there has been increasing attention and demand for CF_3-containing chiral drugs. Substitution of a methyl group by a trifluoromethyl group generally influences the biologic activity by changing the molecule's solubility, lipophilicity, and electronic properties. An especially interesting example is Merck's anti-HIV drug Efavirenz (**1**) and its related compound **2**, which contain a trifluoromethyl group at the tetrasubstituted chiral center at a propargyl position (Figure 1).[9] Inspired by the structure of Efavirenz,

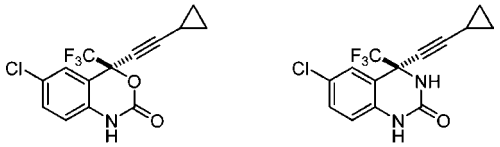


Figure 1. Examples of biologically significant molecules containing CF_3-substituted tetrasubstituted carbons.

we began a project toward developing a direct catalytic enantioselective alkynylation of trifluoromethyl ketones. Although there have been several excellent catalytic enantioselective alkynylations of aldehydes and aldimines reported after the pioneering work of Carreira,[10] none of the methods have been applied to trifluoromethyl ketones.

To establish the basic conditions of catalytic alkynylation of trifluoromethyl ketones, we focused on the unique Brønsted basic characteristic of copper(I) alkoxide.[11] Previously, we developed a catalytic enantioselective direct nitrile−aldol reaction of aldehydes using a copper alkoxide−chiral phosphine complex catalyst.[12] This reaction proceeded through nucleophile generation in situ via selective deprotonation from nitriles ($pK_a \approx 31$ in DMSO) by copper alkoxide, even in the presence of aliphatic aldehydes containing more acidic α-protons ($pK_a \approx 23$). The selective deprotonation was attributed to the selective coordination of soft nitriles to the soft metal,[13] copper. On the basis of those previous studies, we expected that "soft" alkynes ($pK_a \approx 29$) would be selectively activated (deprotonated) by copper alkoxide catalyst in the presence of trifluoromethyl ketones ($pK_a \approx 15$). Indeed, copper alkynide formation by mixing terminal alkynes and copper salts is well-established in coupling reactions, such as the Castro−Stephens reaction,[14] Glaser coupling,[15] and Sonogashira coupling.[16] The copper alkynides generated under *catalytic in metal* conditions, however, have not been utilized in alkynylation of carbonyl groups.[17,18]

The reaction between trifluoroacetophenone (**3a**) and phenylacetylene (**4a**; 2 equiv) was first studied with use of CuO^{t}Bu (10 mol %; prepared in situ from CuOTf·1/2benzene and KO^{t}Bu[12b]) as a catalyst. Only a trace amount of product (**5aa**) was formed in the absence of any ligands (yield = 2%, THF, 60 °C, 22 h). Because the ligands can enhance the nucleophilicity of copper alkynides, we next examined the effects of phosphine ligands.[19] Xantphos was determined to be the optimum ligand; product **5aa** was obtained in a quantitative yield in the presence of the CuO^{t}Bu−xantphos complex (Table 1, entry 1). The reaction has a wide substrate scope with regard to the trifluoromethyl ketones and alkynes (Table 1). Therefore, chemoselective deprotonation from alkynes by the soft metal (copper) alkoxide catalyst and the subsequent addition of the in situ generated copper alkynides to trifluoromethyl ketones were realized. It is noteworthy

(6) For catalytic enantioselective synthesis of CF_3-substituted tertiary alcohols or amines, see: (a) Wang, X.-J.; Zhao, Y.; Liu, J.-T. *Org. Lett.* **2007**, *9*, 1343−1345. (b) Lauzon, C.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2743−2745. (c) Martina, S. L. X.; Jagat, R. B. C.; de Vries, J. G.; Feringa, B.; Minnaard, A. J. *Chem. Commun.* **2006**, 4093−4095. (d) Motoki, R.; Tomita, D.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 8083−8086.

(7) Highly electrophilic trifluoropyruvates have been used as substrates for catalytic enantioselective Friedel−Crafts reaction (7a), ene reaction (7b), and direct aldol reaction (7c). For examples, see: (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550−556. (b) Mikami, K.; Kakuno, H.; Aikawa, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7257−7260. (c) Gathergood, N.; Juhl, K.; Poulsen, T. B.; Thordrup, K.; Jørgensen, K. A. *Org. Biomol. Chem.* **2004**, *2*, 1077−1085.

(8) Catalytic asymmetric trifluoromethylation (8a) and dihydroxylation (8b) are alternative methods. For reviews, see: (a) Billard, T.; Langlois, B. R. *Eur. J. Org. Chem.* **2007**, 891−897. (b) Herrmann, W. A.; Eder, S. J.; Scherer, W. *Angew. Chem., Int. Ed.* **1992**, *31*, 1345−1347.

(9) Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Gearhart, L. A.; Magnus, N. A.; Bacheler, L. T.; Diamond, S.; Jeffrey, S.; Klabe, R. M.; Cordova, B. C.; Garber, S.; Logue, K.; Trainor, G. L.; Anderson, P. S.; Erickson-Vittanen, S. K. *J. Med. Chem.* **2000**, *43*, 2019−2030.

(10) Selected examples of catalytic enantioselective alkynylation of aldehydes: (a) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687−9688. (b) Fässler, C. S.; Tomooka, C. S.; Frantz, D. E.; Carreira, E. M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5843−5845. (c) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760−13761. (d) Yamashita, M.; Yamada, K.-i.; Tomioka, K. *Adv. Synth. Catal.* **2005**, *347*, 1649−1652. (e) Emmerson, D. P. G.; Hems, W. P.; Davis, B. G. *Org. Lett.* **2006**, *8*, 207−210. Selected examples of catalytic asymmetric alkynylation of simple ketones with a *stoichiometric* amount of zinc alkynides: (f) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895−2898. (g) Lu, G.; Li, X.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5057−5058. Selected examples of catalytic enantioselective alkynylation of imines: (h) Wei, C.; Li, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 5638−5639. (i) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763−5766. (j) Bisai, A.; Singh, V. K. *Org. Lett.* **2006**, *8*, 2405−2408.

(11) Tsuda, T.; Hashimoto, T.; Saegusa, T. *J. Am. Chem. Soc.* **1972**, *94*, 658−659.

(12) (a) Suto, Y.; Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3147−3150. (b) Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757−3760.

(13) For similar approaches, see: (a) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 13632−13633. (b) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Tetrahedron* **2007**, doi: 10.1016/j.tet.2007.04.051. (c) Fan, L.; Ozerov, O. V. *Chem. Commun.* **2005**, 4450−4451.

(14) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, 3313−3315.

(15) Glaser, C. *Ber.* **1869**, *2*, 422−424.

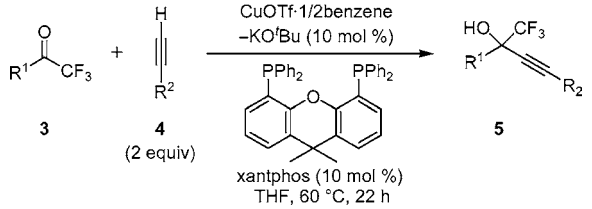
(16) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron, Lett.* **1975**, *16*, 4467−4470.

(17) Addition reactions of copper alkynides to acid chlorides have been reported: (a) Normant, J. F.; Bourgain, M. *Tetrahedron Lett.* **1970**, 2659−2662. (b) Lewis, M. D.; Duffy, J. P.; Heck, J. V.; Menes, R. *Tetrahedron Lett.* **1988**, *29*, 2279−2282. In very rare cases, alkynyl cuprates react with reactive ketones, including a trifluoromethyl alkynyl ketone. (c) Linderman, R. J.; Lonikar, M. S. *J. Org. Chem.* **1988**, *53*, 6013. (d) Palmisano, G.; Pellegata, R. *J. Chem. Soc., Chem. Commun.* **1975**, 892−893. These reactions utilized a stoichiometric amount of copper species.

(18) Catalytic enantioselective conjugate alkynylation of in situ prepared copper alkynides has been reported: (a) Knöpfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 6054−6055. (b) Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682−9683. (c) Fujimori, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4964−4967. For examples of catalytic enantioselective addition of copper alkynides to imines, see refs 10h and 10j.

(19) See the Supporting Information for details. KO^{t}Bu itself (in the absence of Cu salt) did not promote the reaction at all.

Table 1. Alkynylation of Trifluoromethyl Ketones with CuO^{t}Bu−Xantphos Catalyst



entry	ketone (R^1)	alkyne (R^2)	yield (%)[a]
1	**3a** (Ph)	**4a** (Ph)	>99
2	**3a** (Ph)	**4b** (Ph(CH$_2$)$_2$)	>99
3	**3a** (Ph)	**4c** (Et$_3$Si)	71[b]
4	**3b** (Ph(CH$_2$)$_2$)	**4a** (Ph)	>99
5	**3b** (Ph(CH$_2$)$_2$)	**4b** (Ph(CH$_2$)$_2$)	76

[a] NMR yield with $(CHCl_2)_2$ as an internal standard. [b] Isolated yield. 40% of **5ac** (free OH) and 31% of *O*-triethylsilylated product were obtained.

that in entry 3 the alkyne deprotonation was a more favorable pathway than the transmetalation pathway.[6d] To our knowledge, this is the first example of a catalytic alkynylation of trifluoromethyl ketones.

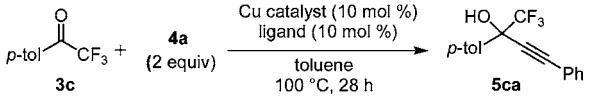
Before extending these conditions to a catalytic enantioselective variant, we next investigated the use of amine ligands. Structural modification of amine ligands is generally much easier than that of phosphine ligands. This fact will be important when ligand structure tuning is necessary for the enantioselective reaction. In addition, we used air-stable $Cu(OTf)_2$ as a source of Cu(I)O^{t}Bu to avoid having to use a glove box manipulation. Cu(II) should be reduced to Cu(I) by terminal alkynes during the reaction.[20]

Three findings are noteworthy in the Cu(II)−diamine *pre*catalyst system (Table 2): (1) There was again significant ligand acceleration in this system (entries 1−4). In the absence of any ligands, product **5ca** was produced in only 12% yield (entry 1). By contrast, yield was improved up to 94% in the presence of bipyridine-type ligands, especially phenanthroline (**7**: entry 3). Use of trivalent terpyridine (**8**), however, markedly decreased the yield (entry 4). Cu(I) alkoxide is likely the actual catalyst because a comparable yield was obtained with Cu(I)O^{t}Bu (entry 5). (2) A catalyst prepared from $Cu(OTf)_2$ and KO^{t}Bu in a 1:2 ratio produced higher activity than that prepared from a 1:1 combination of $Cu(OTf)_2$ and KO^{t}Bu (entry 3 vs 6). (3) The presence of KOTf (generated as a side product in the copper alkoxide generation step) improved product yield (entries 7−11).[21] By using commercially available $Cu(OMe)_2$ in the presence of phenanthroline produced **5ca** in only 54% (entry 7), the yield was improved to 73% when 20 mol % of KOTf was added (entry 8). In addition, the product was obtained only

(20) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632−2657.

(21) The actual catalyst might be a bimetallic complex (or higher aggregates) of Cu and K. For an example of a Cu−K bimetallic complex, see: (a) Ahlrichs, R.; Anson, C. E.; Fenske, D.; Hampe, O.; Rothenberger, A.; Sierka, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4036−4029. (b) Heller, M.; Sheldrick, W. S. *Z. Anorg. Allg. Chem.* **2004**, *630*, 1191−1195.

Table 2. Optimization of Alkynylation of Trifluoromethyl Ketone with Cu(II)−Diamine *Pre*catalyst



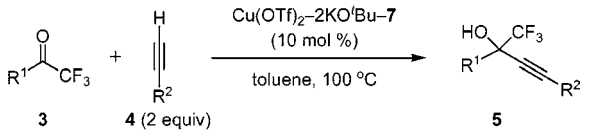
entry	ligand[a]	catalyst	yield[b] (%)
1	none	$Cu(OTf)_2$−2KO^{t}Bu	12
2	**6**	$Cu(OTf)_2$−2KO^{t}Bu	61
3	**7**	$Cu(OTf)_2$−2KO^{t}Bu	94[c]
4	**8**	$Cu(OTf)_2$−2KO^{t}Bu	6
5	**7**	CuOTf·1/2benzene−KO^{t}Bu	94
6	**7**	$Cu(OTf)_2$−KO^{t}Bu	78
7	**7**	$Cu(OMe)_2$	54
8	**7**	$Cu(OMe)_2$−2KOTf	73
9	**7**	$Cu(OTf)_2$−2LiO^{t}Bu	13
10	**7**	$Cu(OTf)_2$−2NaO^{t}Bu	66
11	**7**	$Cu(OTf)_2$−2CsO^{t}Bu	40

[a] **6**: 2,2′-bipyridyl. **7**: 1,10-phenanthroline. **8**: 2,2′:6′2″-terpyridine. [b] NMR yield with $(CHCl_2)_2$ as an internal standard. [c] Isolated yield.

in moderate yield when copper alkoxide catalyst was prepared from $Cu(OTf)_2$ and alkaline metal *tert*-butoxides other than KO^{t}Bu (entries 9−11).

We then examined the substrate generality of the Cu−diamine catalysis under the optimized conditions (Table 3).

Table 3. Alkynylation of Trifluoromethyl Ketones with a Cu−Diamine Catalyst



entry	ketone (R^1)	alkyne (R^2)	time (h)	yield (%)[a]
1	**3a** (Ph)	**4a** (Ph)	14	95
2	**3c** (*p*-Me-C$_6$H$_4$)	**4a** (Ph)	28	94
3	**3d** (*p*-MeO-C$_6$H$_4$)	**4a** (Ph)	45	75
4	**3e** (*p*-Cl-C$_6$H$_4$)	**4a** (Ph)	27	91
5	**3f** (*p*-Br-C$_6$H$_4$)	**4a** (Ph)	17	72
6	**3i** (*o*-Me-C$_6$H$_4$)	**4a** (Ph)	20	70
7	**3j** (*m*-Me-C$_6$H$_4$)	**4a** (Ph)	22	81
8	**3g** (3-thiophene)	**4a** (Ph)	17	79
9	**3b** (Ph(CH$_2$)$_2$)	**4a** (Ph)	26	96
10	**3h** (CH$_3$(CH$_2$)$_9$)	**4a** (Ph)	16	87
11	**3k** (*c*-Hex)	**4a** (Ph)	12	73
12	**3a** (Ph)	**4b** (Ph(CH$_2$)$_2$)	14	80
13	**3a** (Ph)	**4c** (Et$_3$Si)	24	80[b,c]
14	**3b** (Ph(CH$_2$)$_2$)	**4b** (Ph(CH$_2$)$_2$)	20	95
15	**3b** (Ph(CH$_2$)$_2$)	**4c** (Et$_3$Si)	20	86[d]

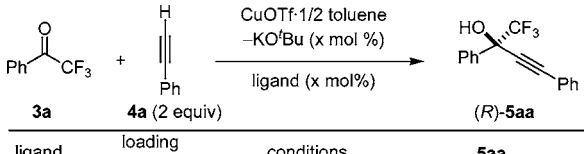
[a] Isolated yield. [b] *O*-Triethylsilylated product was obtained. [c] NMR yield with $(CHCl_2)_2$ as an internal standard. [d] Combined yield of **5bc** (75%) and the corresponding *O*-triethylsilylated product (11%).

High reactivity was consistently observed when aromatic (entries 1−7), heteroaromatic (entry 8), and enolizable aliphatic trifluoromethyl ketones (entries 9−11) were used

as electrophiles. In addition, various alkynes, including phenylacetylene (**4a**), alkylacetylene (**4b**), and synthetically useful silylacetylene (**4c**), were applicable.

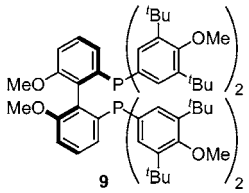
The described reactions could, in principle, be extended to a catalytic enantioselective reaction. Screening several available ligands indicated that DTBM-SEGPHOS (**9**) and pybox **10** are promising chiral ligands (Scheme 1). Thus,

Scheme 1. Preliminary Extension to Catalytic Enantioselective Alkynylation of Trifluoromethyl Ketones



3a **4a** (2 equiv) (*R*)-**5aa**

ligand	loading (x mol %)	conditions	**5aa**
9	10	60 °C, 21 h	>99%, 42% ee (*R*)
10	10	100 °C, 18 h	43%, 49% ee (*S*)
10	20	100 °C, 16 h	66%, 52% ee (*S*)



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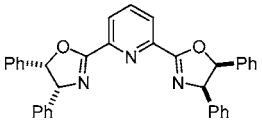
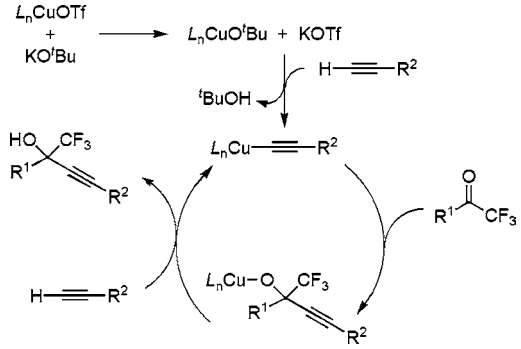


10

with Cu−**9** as a catalyst (10 mol %), product **5aa** was obtained in greater than 99% yield with 42% ee. On the other hand, the Cu−**10** complex afforded **5aa** in 43% yield with 49% ee (10 mol % of catalyst), and 66% yield with 52% ee (20 mol % of catalyst).[22] Although enantioselectivity is moderate at this stage, this catalytic enantioselective direct alkynylation of trifluoromethyl ketones is a new entry for the construction of enantiomerically enriched tertiary CF_3-substituted propargyl alcohols.

Although the detailed reaction mechanism (especially, the origin of the beneficial effect of KOTf) remains unclear, the reaction likely proceeds via copper alkynides, which are generated in situ through chemoselective deprotonation of alkynes by copper alkoxide. This hypothesis is partially supported by the following result. When commercially available copper phenylacetylide was used as a catalyst (10 mol %) in the presence of **9**, product **5aa** was produced with comparable enantioselectivity (43% ee[23] vs 42% ee in Scheme 1) and reactivity as when using CuOTf−KO^{t}Bu−**9** as a catalyst. On the basis of this result, we propose the catalytic cycle as shown in Scheme 2. Selective activation

Scheme 2. Proposed Catalytic Cycle



of alkynes by the soft metal (Cu)−soft alkyne π orbital interactions and the enhanced nucleophilicity of the resulting copper alkynide by the ligands are key to the success of this catalytic cycle.

In summary, we achieved the first general catalytic alkynylation of trifluoromethyl ketones using a copper alkoxide−diphosphine or diamine complex. This process is an atom-economic C−C bond-formation, which proceeds through proton transfer from teminal alkynes to the product tertiary alcohol. The methodology can be a platform for catalytic enantioselective synthesis of CF_3-substituted tertiary propargyl alcohols, which are important chiral building blocks for pharmaceuticals. Further studies focusing on improving the enantioselectivity are ongoing.

Acknowledgment. Financial support was provided by a Grant-in-Aid for Specially Promoted Research of MEXT. R.M. thanks JSPS for the research fellowships. We thank Mr. H. Morimoto for the calculation of pK_a value of trifluoromethyl ketones.

Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL071003K

(22) Cu(I)OTf was used as the copper source in the catalytic enantioselective reactions. When Cu(II)$(OTf)_2$−2KO^{t}Bu was used as a *pre*catalyst in combination with pybox **10**, the results were variable in each run.

(23) 5 mol % of KOTf was added to the reaction mixture. In the absence of KOTf, copper phenylacetylide−**9** catalyst produced **5aa** with 38% ee. Therefore, the addition of KOTf slightly improved the enantioselectivity.