JOC *Note*

Highly Regioselective Coupling Reactions of Allylic and Propargylic Alcohol Derivatives with γ,γ-Dialkoxyallylic Zirconium Species via Zr-to-Cu Transmetalation

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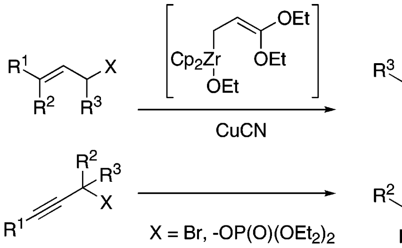
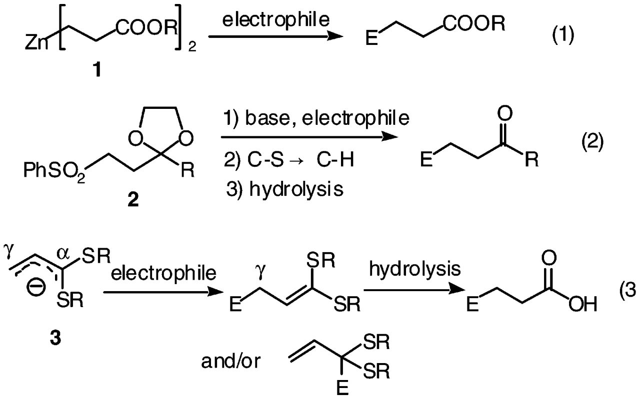


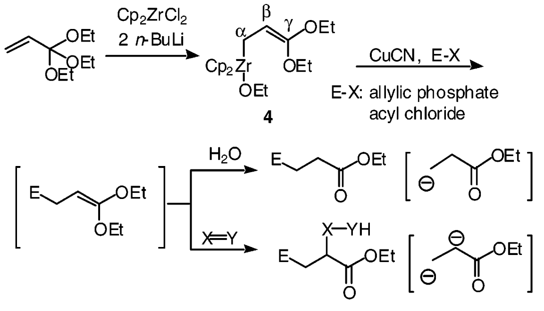
In the presence of CuCN, reaction of γ,γ-dialkoxyallylic zirconium species **4**, generated in situ by treating triethyl orthoacrylate with zirconocene−butene complex, with allylic and propargylic phosphates proceeded at the α-position of **4** in a highly S_N2'-selective manner to give the corresponding 5-alkenoates and 4,5-alkadienoates, respectively. In the present Cu(I)-mediated coupling reaction, the γ,γ-dialkoxyallylic zirconium species **4** serves as a synthetically useful homoenolate anion equivalent of propionate.

Homoenolate anion and its equivalent organometals, which function as an inverse polarity of Michael acceptor, are important synthons in organic synthesis.[1] In this area, the zinc homoenolate of propionate **1** has been demonstrated to have versatile reactivity with general synthetic utility.[2,3] Another typical example developed as homoenolate anion equivalents may be the conceptually important umpolung of carbonyl reactivity with sulfur-substituted nucleophiles such as the carbonyl-protected β-phenylsulfonyl ketone **2**[4] or allylic anion of dithioacetal **3** and allyl sulfides[5] (Scheme 1). However, in this sulfur-based chemistry there exists several disadvantages, in particular, due to the lack of regioselectivity (γ vs α position of the allyl system) in the reactions with electrophiles and due to the requirement of the cleavage of carbon−sulfur bond under specific conditions, which often affects on the yields of the products.

SCHEME 1



SCHEME 2



In our preliminary report, we have shown that γ,γ-dialkoxyallylic zirconium species **4**,[6] easily formed in situ by treating triethyl orthoacrylate with zirconocene−butene complex, can serve as a new homoenolate or α,β-dianion equivalent of propionate in the CuCN-mediated cross-coupling reaction with allylic phosphates or acid chlorides (Scheme 2).[7] Thus, the Cu(I)-mediated reaction of γ,γ-dialkoxyallylic zirconium species **4** proceeded regioselectively at its α-position, while we had already reported both γ-selective and β-selective reactions of this allylic zirconium species **4** with carbonyl compounds (Scheme 3).[6,8] The results obtained from the reactions with carbonyl compounds indicated that depending on

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[†] Tokyo University of Pharmacy and Life Science.

[1] For reviews on homoenolate anions and homoenolate anion equivalents, see: (a) Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205. (b) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932. (c) Ryu, I.; Sonoda, N. *J. Org. Synth. Chem. Jpn.* **1985**, *43*, 112. (d) Kuwajima, I.; Nakamura. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergmon Press: Oxford, 1991; Vol. 2, Chapter 1.14.

[2] (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368. (b) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056 and references cited therein.

[3] For recent examples of homoaldol reactions, see: (a) Martin, E. O.; Gleason, J. L. *Org. Lett.* **1999**, *1*, 1643. (b) Ahlbrecht, H.; Beyer, U. *Synthesis* **1999**, 365. (c) Hanazawa, T.; Okamoto, S.; Sato, F. *Org. Lett.* **2000**, *2*, 2369.

[4] (a) Kondo, K.; Tunemoto, D. *Tetrahedron Lett.* **1975**, *1007*, 1397 and 2275. (b) Julia, M.; Badet, B. *Bull. Soc. Chim. Fr.* **1975**, 1363.

[5] (a) Grobel, B.-T.; Seebach, D. *Synthesis* **1977**, 357. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. (c) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932. (d) Ziegler, F. E.; Tam, C. C. *J. Org. Chem.* **1979**, *44*, 3428. (e) Bellato, R.; Gatti, A.; Venturello, P. *Tetrahedron* **1992**, *48*, 2501.

[6] (a) Ito, H.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 5829. (b) Sato, A.; Ito, H.; Taguchi, T. *J. Org. Chem.* **2000**, *65*, 918.

[7] Sato, A.; Ito, H.; Yamaguchi, Y.; Taguchi, T. *Tetrahedron Lett.* **2000**, *41*, 10239.

10.1021/jo0489216 CCC: $30.25

SCHEME 3

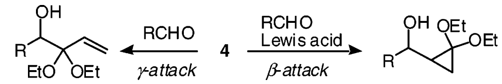
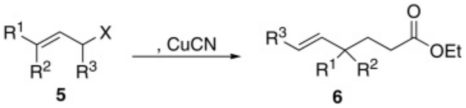


TABLE 1. CuCN-Mediated Coupling Reaction of 4 with Allylic Substrate[a]



5

6

entry	R^1	R^2	R^3	X	6	yield[b] (%)
1	H	H	H	Br	**6a**	72
2	H	H	H	$OP(O)(OEt)_2$	**6a**	83
3	H	H	H	OAc or OBz	**6a**	0
4	H	H	$PhCH_2CH_2$	$OP(O)(OEt)_2$	**6b**	81[c]
5	CH_3	H	H	$OP(O)(OEt)_2$	**6c**	74
6	$PhCH_2CH_2$	CH_3	H	$OP(O)(OEt)_2$	**6d**	96

[a] Solvent: toluene–THF (1:3); 1 equiv of CuCN. [b] Isolated yield. [c] $E/Z = 2.0$.

the reaction conditions the zirconium species **4** can act as an α,β-unsaturated acyl anion equivalent and *gem*-dialkoxycyclopropyl anion equivalent, respectively.[6,8] Since the coupling reaction of **4** with allylic phosphates or acid chlorides did not proceed without CuCN, we believe that the cross-coupling reaction should proceed through Zr-to-Cu transmetalation generating dialkoxyallylic copper species as the plausible intermediate.[9] Further study of the present coupling reaction has been made to see the reactivity and regioselectivity with propargylic and allenyl alcohol derivatives as well as stereochemical outcome with chiral allylic and propargylic phosphates. The results are reported in this paper.

Reaction with Allylic Substrates. Treatment of γ,γ-dialkoxyallylic zirconium species **4**, generated from triethyl orthoacrylate and zirconocene–butene complex in toluene, with CuCN followed by the reaction with allylic phosphates **5** in toluene–THF (1:3–4 v/v) proceeded at the α-position of **4** in a highly S_N2' manner to give the 5-alkenoate **6** in good yields.[7] Typical results are summarized in Table 1. Allyl bromide and allyl diethyl phosphate gave the coupling product **6a** in 72% and 83% yield, respectively, but allyl acetate or benzoate did not afford the coupling product **6a**; instead the starting ester was recovered (entries 1–3). Contrary to allyl bromide which gave the coupling product **6a**, substituted allylic bromides such as cinnamyl bromide gave a complex mixture under the similar reaction conditions.[7] Thus, allylic phosphates rather than bromides are recommended as the partner for the present coupling reaction not only due to the reactivity but also due to availability and ease of preparation.[10] As shown in Table 1, with the substituted allylic phosphates, S_N2' products **6** reacted at the α-position of the zirconium species **4** were exclusively formed in good yields, even in the case of terminally disubstituted primary allylic phosphates (entries 4–6).[9d,11,12] A moderate *E* selectivity of the coupling product **6b** ($E/Z = 2$) was observed with the secondary allylic phosphate (entry 4). No coupling product was obtained with primary alkyl iodides, benzyl bromide and alkenyl iodides. Sterically bulky geminal alkoxyl substitutents in the dialkoxyallyic copper species effects the selective coupling at the α-position and at the same time its relatively low reactivity. This would be a sharp contrast to monosubstituted allylic cuprate such as cinnamyl derivative, which reacted with primary alkyl halide exclusively at the γ-position.[9g]

In these coupling reactions conducted in a mixture of THF and toluene (3–4:1 v/v) or in THF, the efficiency of CuCN as compared with the other commonly used Cu(I) salts such as CuI, CuI·2LiCl, CuBr, $CuBr·Me_2S$, or CuCl was remarkable to obtain the desired products **6**.[13] Furthermore, the reaction temperature seemed to be a crucial factor for the Cu(I)-mediated coupling reactions examined here. When the temperature rose to about −20 °C after addition of CuCN (1 equiv) to a yellowish solution of dialkoxyallylic zirconium **4**[6] in THF–toluene at −78 °C, the reaction mixture changed to a green-colored clear solution. When this green solution stood at room temperature (ca 25 °C), the color gradually changed from green to dark deep yellow and at the same time black precipitates such as copper mirror appeared on the flask wall. Addition of allyl phosphate at this stage resulted in the recovery of the phosphate without the formation of the coupling product. Thus, the observed color change may indicate that the copper species has a short lifetime at room temperature. With allylic phosphates **5**, coupling reaction hardly proceeded at low temperature below −30 °C and very slowly at −10 to 0 °C. Thus, the reactivity of the copper species formed from **4** by Zr-to-Cu transmetalation using CuCN (1 equiv) seemed considerably low, and finally, for the coupling reaction we optimized the reaction temperature at 0–15 °C and reaction time within about 10 h. According to Lipshutz's report on cuprate-mediated coupling reaction of allylic zirconium,[9g] we examined transmetalation by higher order cuprate

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(8) For reaction of γ,γ-dialkoxyallylic zirconium species **4** with carbonyl compounds, see: (a) Ito, H.; Kuroi, H.; Ding, H.; Taguchi, T. *J. Am. Chem. Soc.* **1998**, *120*, 6623. (b) Ito, H.; Sato, A.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 3217. (c) Ito, H.; Sato, A.; Kusanagi, T.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 3397. See also ref 6.

(9) For examples of zirconium to copper transmetalation, see: (a) Yoshifuji, M.; Loots, M. J.; Schwartz, J. *Tetrahedron Lett.* **1977**, 1303. (b) Wipf, P.; Smitrovitch, J. H. *J. Org. Chem.* **1991**, *56*, 6494. (c) Lipshutz, B. H.; Dimock, S. H. *J. Org. Chem.* **1991**, *56*, 5761. (d) Venanzi, L. M.; Lehmann, R.; Keil, R.; Lipshutz, B. H. *Tetrahedron Lett.* **1992**, *33*, 5857. (e) Wipf. D. *Synthesis* **1993**, 537. (f) Lipshutz, B. H.; Wood, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 12625. (g) Lipshutz, B. H.; Bhandari, A.; Lindsley, C.; Keil, R.; Wood, M. R. *Pure Appl. Chem.* **1994**, *66*, 1493. (h) Lipshutz, B. H.; Segi, M. *Tetrahedron* **1995**, *51*, 4407. (i) Fleming, S.; Kabbara, J.; Nickiseh, K.; Westermann,; Mohr, J. *Synlett* **1995**, 183. (j) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853. (k) Takahashi, T.; Shen, B.; Nakajima, K.; Xi, Z. *J. Org. Chem.* **1999**, *64*, 8706. (l) Hanzawa, Y.; Narita, K.; Taguchi, T. *Tetrahedron Lett.* **2000**, *41*, 109.

(10) Miller, J. A.; Wood, H. C. S. *J. Chem. Soc.* **1968**, 1837.

(11) For examples of allylic cuprate reactions, see: (a) Lipshutz, B. H.; Elworthy, T. R. *J. Org. Chem.* **1990**, *55*, 1695. (b) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1990**, *112*, 4404. (c) Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 251. See also: (d) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

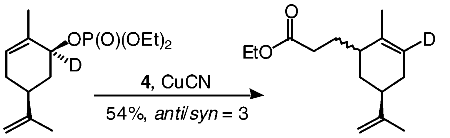
(12) For reviews of organocopper reagents, see: (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (b) Posner, G. H. *Org. React.* **1975**, *22*, 253.

(13) Efficiency of CuCN as a precursor for cuprate formation was reported. (a) Bertz, S. H.; Gibson, C. P.; Dabbagh, G. *Tetrahedron Lett.* **1987**, *28*, 4251. (b) Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884. (c) Tseng, C. C.; Yen, S.-J. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2892. See also ref 9i.

$[Me_2Cu(CN)Li_2]$ in stead of CuCN, but lower yield of the product **6** was the result. It should be noted that the coupling products **6** can be obtained in good yields even on using nearly equal amount of the allylic zirconium **4** relative to the phosphates (see the Supporting Information), since generally an excess amount of allylic metals is used in such coupling reactions to obtain the products in good yields.[12]

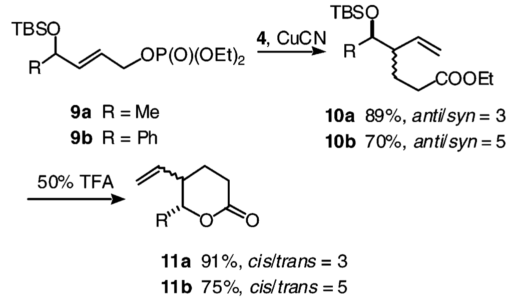
The stereochemical outcomes of the present coupling reactions with chiral allylic substrates, *cis*-carvyl phosphate **7** and 4-alkoxy-2-alkenyl phosphate **9**, were also examined. Reaction of 1-deuterated *cis*-carvyl phosphate **7**[11c,14,15] with **4** in the presence of CuCN in THF at 0 °C proceeded in completely regioselective manner to give the S_N2' product **8** in 54% yield, but with moderate *anti*-selectivity (*anti*/*syn* = 3) (Scheme 4).

SCHEME 4



7 **8**

SCHEME 5

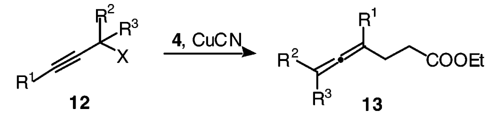


9a R = Me
9b R = Ph

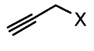
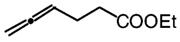
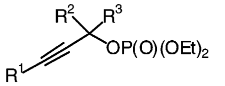
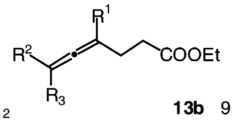
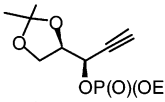
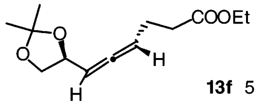
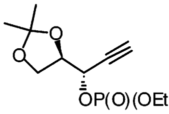
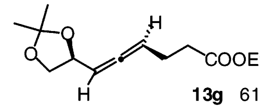
10a 89%, *anti*/*syn* = 3
10b 70%, *anti*/*syn* = 5

11a 91%, *cis*/*trans* = 3
11b 75%, *cis*/*trans* = 5

TABLE 2. CuCN-Mediated Coupling Reaction of 4 with Propargylic Substrate[a]



12 **13**

Entry	12	13		Yield (%)
1	 X = Br			75
2	OTs		**13a**	85
3	OP(O)(OEt)$_2$			75
				
4	R^1=R^3=H R^2=$PhCH_2CH_2$		**13b**	92 [b]
5	R^1=H R^2=R^3=CH_3		**13c**	64
6	R^1=$PhCH_2CH_2CH_2$ R^2=R^3=H		**13d**	86 [b]
7	R^1=$PhCH_2CH_2CH_2$ R^2=CH_3 R^3=H		**13e**	93
8			**13f**	54
9			**13g**	61

[a] Solvent: toluene−THF (1:3); 1 equiv of CuCN. [b] Solvent: toluene.

With racemic 4-*tert*-butyldimethylsilyloxy-2-pentenyl phosphate derivative **9a**, reaction proceeded in completely S_N2' manner to obtain the product **10a** in 89% yield as a mixture of diastereomers in a ratio of 3:1. For the determination of relative stereochemistry, **10a** was converted to the lactone form by treating with 50% aqueous trifluoroacetic acid to give the 5,6-disubstituted δ-varelolactone **11a** (91% yield, ratio 3:1) (Scheme 5). From the ^1H NMR spectrum of each isomer, the major isomer was confirmed to be ***cis*-11a** having vicinal coupling constant $J_{H(5)-H(6)} = 3.6$ Hz, whereas 6.3 Hz for the minor isomer ***trans*-11a**. Thus, the major diastereomer of **10a** was assigned as an *anti* isomer. Under similar conditions, the phenyl derivative **9b** showed a slightly higher *anti* selectivity to give the coupling product **10b** in 70% yield (*anti*/*syn* = 5). Conversion to the lactone compound **11b** also proceeded in a good yield (Scheme 5). It is well documented that in reactions of organocopper reagents with a chiral allylic substrate having an oxygen-substituted stereogenic center at 4-position and the leaving group at 1-position such as phosphates **9** or the corresponding chloride, regioselectivity (S_N2 vs S_N2') strongly depends on the nature of organocopper reagent, but a high to excellent *anti* diastereoselectivity in the S_N2' product is observed regardless the nature of the copper reagent.[14] Contrary to these, with allylic phosphates such as **7** and **9**, the present copper reagent formed from CuCN and the dialkoxyallylic zirconium **4** in THF showed an excellent regioselectivity reacting at the α-position of **4** in a complete S_N2' manner, but with moderate diastereoselectivity.

Reaction with Propargylic Substrates. Substitution reaction of propargylic substrates with organocopper reagents or with organometallics in the presence of Cu(I)X provides the corresponding allenyl products in an S_N2' manner.[12] Not surprisingly, CuCN-mediated coupling reaction of the dialkoxyallylic zirconium **4** with propargylic phosphates **12** also proceeded at the α-position of **4** in a completely S_N2' manner to give the 4,5-alkadienoates **13** in good yields (Table 2). Propargyl phosphate as well as bromide or tosylate can be used giving rise to the coupling product **13a** (entries 1−3). With the substrates having alkyl substituents, the coupling reaction also proceeded smoothly to give the allenyl

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(14) (a) Arai, M.; Nakamura, E.; Lipshutz, B. H. *J. Org. Chem.* **1991**, *56*, 5489. (b) Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* **1989**, *111*, 3091. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (c) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.

(15) Itoh, A.; Ozawa, S.; Oshima, K.; Sasaki, S.; Yamamoto, H.; Hiyama, T.; Nozaki, H. *Bull Chem. Soc. Jpn.* **1980**, *53*, 2357.

(16) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349.

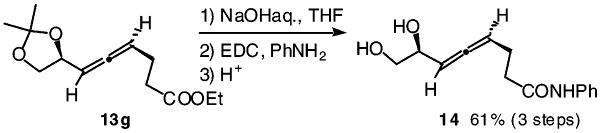
(17) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.

(18) (a) Ochiai, H.; Tamaru, Y.; Tsubaki, K.; Yoshida, Z. *J. Org. Chem.* **1987**, *52*, 4418. (b) Kasatkin, A.; Kobayashi, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 1849.

(19) Stepanyan, A. N.; Oganyan, G. B.; Badanyan, Sh. O. *Arm. Khim. Zh.* **1987**, *40*, 122.

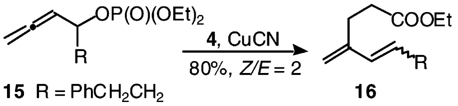
compounds **13b**−**e** in good yields regardless of the alkyl-substitution pattern (entries 4−7). Each diastereomerically pure phosphate (**12f** and **12g**) derived from (*R*)-glyceraldehyde acetonide gave the corresponding allenyl compound (**13f** and **13g**) as a single isomer, respectively. The absolute stereochemistry of **13g** was determined by X-ray analysis of amide **14** which was easily obtained in three steps from **13g** (Scheme 6).

SCHEME 6



With allenyl phosphate **15**, the 1,3-dienyl compound **16** was exclusively formed in 80% yield with little stereoselectivity (*Z*/*E* = 2) (Scheme 7).

SCHEME 7



In conclusion, we have shown that in the presence of CuCN reaction of γ,γ-dialkoxyallylic zirconium species **4** with allylic and propargylic phosphates proceeds at the α-position of **4** in an S_N2' manner to give the 5-alkenoate or 4,5-alkadienoate derivatives in good yield. In this reaction, the zirconium species **4** acts as a synthetically useful homoenolate anion equivalent of propionate.

Supporting Information Available: Experimental procedure and characterization of new compounds **9a**,**b**, **12f**,**g**, **15**, **6b**−**d**, **8**, **10a**,**b**, **13b**−**g**, **16**, **11a**,**b**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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