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 $S_N 2'$ -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 sulfursubstituted nucleophiles such as the carbonyl-protected

 β -phenylsulfonyl ketone 2^4 or allylic anion of dithioacetal 3 and allyl sulfides⁵ (Scheme 1). However, in this sulfur-

SCHEME 1



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.

In our preliminary report, we have shown that γ,γ dialkoxyallylic zirconium species 4,6 easily formed in situ by treating triethyl orthoacrylate with zirconocenebut ene 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

SCHEME 2



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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SCHEME 3



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

		<u>,</u>	CuCN R ³	0 R ¹ R ² 6	DEt	
entry	R ¹	\mathbb{R}^2	\mathbb{R}^3	X	6	yield ^b (%)
1	Н	Н	Н	Br	6a	72
2	Н	н	Н	OP(O)(OEt) ₂	6a	83
3	Н	Η	Н	OAc or OBz	6a	0
4	Н	н	$PhCH_2CH_2$	OP(O)(OEt) ₂	6b	81^c
5	CH_3	н	Н	$OP(O)(OEt)_2$	6c	74
6	$PhCH_2CH_2$	CH_3	Н	OP(O)(OEt) ₂	6d	96
^{<i>a</i>} Solvent: toluene–THF (1:3); 1 equiv of CuCN. ^{<i>b</i>} Isolated yield. ^{<i>c</i>} $E/Z = 2.0$.						

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 Zrto-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

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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, $S_N 2'$ 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·Me₂S, 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 $^{\circ}$ C and very slowly at -10 to 0 $^{\circ}$ 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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 $[Me_2Cu(CN)Li_2]$ 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



With racemic 4-tert-butyldimethylsilyloxy-2-pentenyl phosphate derivative 9a, reaction proceeded in completely $S_N 2'$ 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 $J_{\rm H(5)-H(6)} = 3.6$ 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 $(S_N 2 \text{ vs } S_N 2')$ strongly depends on the nature of organocopper reagent, but a high to excellent anti diastereoselectivity in the S_N2' product is observed regardless

SCHEME 5







 a Solvent: toluene–THF (1:3); 1 equiv of CuCN. b Solvent: toluene.

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 4,5alkadienoates 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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compounds 13b-e in good yields regardless of the alkylsubstitution 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. JO0489216