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Cu(I)-assisted carbon–carbon bond forming reactions of γ,γ-dialkoxyallylic zirconium species: a new versatile homoenolate equivalent of propionate

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Abstract

In the presence of CuCN, reaction of γ,γ-dialkoxyallylic zirconium species **1** with acyl chloride or allylic phosphates proceeded at the α-position of **1** to give alkanoates **3** after aqueous work-up. The ketene dialkylacetal moiety in the coupling products **2** can be used for further bond forming reaction with electrophiles such as nitrosobenzene, nitrostyrene or trichloroacetylisocyanate. © 2000 Elsevier Science Ltd. All rights reserved.

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We have reported an efficient generation and the characterization of γ,γ-dialkoxyallylic zirconium species **1** and its reaction with a variety of carbonyl compounds. That is; the zirconium species **1**, easily formed in situ by treating orthoester of acrylate with zirconocene–butene complex, reacted with aldehyde at the γ-position as a typical allylic metal to give the *gem*-dialkoxylated homoallyl alcohol derivative,[1] while in the presence of more than 1 equivalent of Lewis acid **1** reacted firstly at the β-position (nucleophilic attack of ketene acetal moiety), followed by carbon–zirconium bond cleavage to give the dialkoxycyclopropane derivative.[2] Furthermore, **1** showed a different reaction pathway in the reaction with acrylamide derivative to give the dialkoxy cyclobutane compounds.[3] As a further development of the synthetic utility of the zirconium species **1**, we focused on examining the cross-coupling reaction at the α-position of **1** leading to a new homoenolate equivalent of propionate.[4–6] In this paper, we report that copper(I) assisted cross-coupling reaction of the zirconium species **1** with acyl chlorides and allylic phosphates proceeds at the α-position of **1** to give the alkanoate derivative **3**. Furthermore, the ketene dialkylacetal moiety in the coupling product **2** can be used for a further bond forming reaction with electrophiles or via cycloaddition reaction (Scheme 1).

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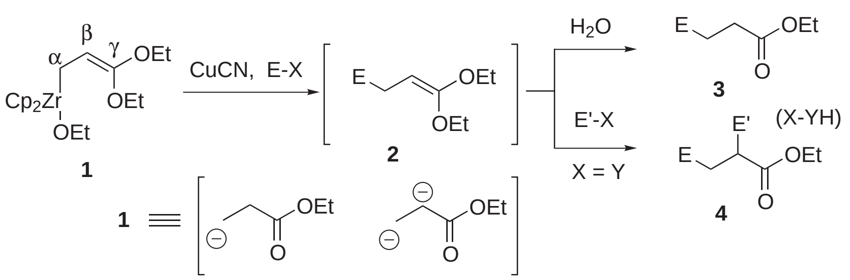
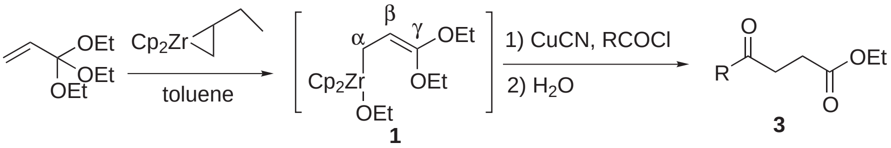


Scheme 1.

Reaction of the zirconium species **1**, generated from triethyl orthoacrylate and zirconocene–butene complex in toluene,[1] with benzoyl chloride was conducted to find a suitable copper salt for the coupling reaction. While copper salt such as CuCl, CuBr, $CuBr{\cdot}Me_2S$, $CuCN{\cdot}2LiCl$, which often work well in the transmetalation of the carbon–zirconium bond,[7] did not give a satisfactory result (mostly giving rise to a complex mixture), CuCN was found to effect the cross-coupling at the α-position of **1** to provide the γ-keto ester **3a** after aqueous work-up.[8] Without CuCN any bond forming product between **1** and benzoyl chloride was not detected. The reaction proceeded by using a catalytic amount of CuCN (20 mol%, **3a** 53%), but the yield of the coupling product **3a** increased to 65% when 1 equiv. of CuCN was used. Not only aromatic acid chloride but also an aliphatic one gave the coupling products, although sterically hindered pivaroyl chloride resulted in low yield (27%) of product **3d** (Scheme 2).

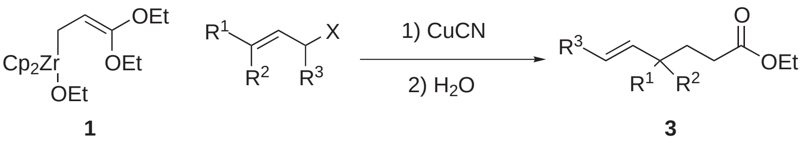


	3a	3b	3c	3d
R	Ph	*p*-NO_2Ph	*n*-C_7H_{15}	*t*-Bu
Yield %	65	50	57	27

Scheme 2.

CuCN catalyzed coupling reaction of **1** also proceeded with allylic bromides or preferably with allylic phosphates. Coupling reactions were carried out in toluene–THF (2:1) using 1 equiv. of CuCN. Results are summarized in Table 1. Allyl bromide and allyl diethyl phosphate gave the coupling product **3e** in 72 and 83% yield, respectively, but **3e** was not obtained with allyl acetate (entries 1–3). Substituted allylic bromides were not always suitable substrates in the present coupling reaction. For example, in the case of cinnamyl bromide a complicated mixture resulted, probably partly due to a halogen–metal exchange reaction. On the other hand, cinnamyl phosphate gave the S_N2' product **3h** in 65% yield along with the formation of the coupling product **5** (15% yield) reacted between the γ-position of **1** and α-position of the phosphate (entries 6, 7).[8] As shown in Table 1, with the other substituted allylic phosphates examined here, S_N2' products reacted at the α-position of the allylic zirconium **1** were exclusively formed in good yields, even in the case of terminally disubstituted primary allylic phosphates (entries 8, 9).[8,9] Thus, low regioselectivity (S_N2' versus S_N2 pathway) in the reaction with

Table 1
CuCN-Assisted coupling reaction of **1** with allylic substrate[a]



Entry	R^1	R^2	R^3	X	**3**	Yield (%)[b]
1	H	H	H	Br	**3e**	72[c]
2	H	H	H	OP(O)(OEt)$_2$	**3e**	83
3	H	H	H	OAc	**3e**	0
4	H	H	CH$_3$	OP(O)(OEt)$_2$	**3f**	75[d]
5	CH$_3$	H	H	OP(O)(OEt)$_2$	**3g**	74
6	Ph	H	H	OP(O)(OEt)$_2$	**3h**	65[e,f]
7	Ph	H	H	Br	**3h**	Trace
8	CH$_3$	CH$_3$	H	OP(O)(OEt)$_2$	**3i**	81
9	PhCH$_2$CH$_2$	CH$_3$	H	OP(O)(OEt)$_2$	**3j**	96

[a] Solvent; toluene–THF (2:1), 1 equiv. CuCN.

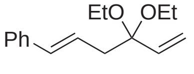
[b] Isolated yield.

[c] 68% yield when 20 mol% CuCN was used.

[d] *E*/*Z*=2.5.

[e] Solvent; toluene.

[f] Isomeric coupling product **5** was isolated in 15% yield.



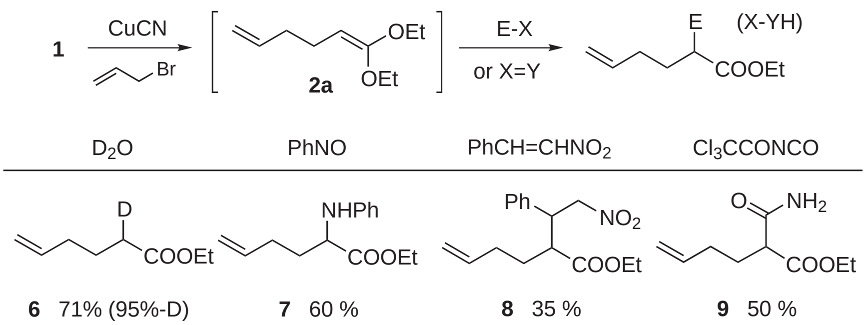
5 15%

cinnamyl phosphate may be an exceptional case. Since coupling reaction of **1** with allylic phosphates did not proceed without CuCN as in the cases of acyl chlorides, in these reactions allylic copper species should be formed through the Zr-to-Cu transmetalation.[10]

Under similar reaction conditions, alkyl iodide (butyl iodide), alkenyl iodide (*E*-1-iodohexene), aryl iodide (iodobenzene), benzyl bromide and benzyl diethylphosphate did not give the coupling products.

To utilize the ketene acetal moiety in the coupling product, we examined the further reaction with electrophiles or with electron deficient unsaturated compounds.[11] Some examples are shown in Scheme 3. Quenching the coupling product **2a** formed from allyl bromide with D_2O provided the α-deuterated ester **6** (71% yield, 95%-D) as expected. Introduction of amino group to the α-position could be achieved by reaction with nitrosobenzene to give the anilino derivative **7** in 60% yield.[12] Furthermore, nitrostyrene gave the corresponding adduct **8** in 35% yield (diastereomer ratio 1.5:1)[11b] and trichloroacetylisocyanate[11c] gave the malonate derivative **9** in 50% yield after the purification of the crude product by silica gel column chromatography.

In conclusion, we have shown that in the presence of CuCN reaction of γ,γ-dialkoxyallylic zirconium species **1** with acyl chloride and allylic phosphates proceeds at the α-position of **1** to



Scheme 3.

give the alkanoates in S_N2' manner with the allylic phosphates. Furthermore, the ketene diethylacetal moiety in the coupling product can be used for further bond forming reaction with electron-deficient unsaturated compounds. Thus, γ,γ-dialkoxyallylic zirconium species **1** can serve as a homoenolate and α,β-dianion equivalents of propionate.[13]

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10. Typical procedure for coupling reaction with allylic phosphate (Table 1, entry 5): Under an argon atmosphere, a mixture of Cp_2ZrCl_2 (351 mg, 1.2 mmol) and *n*-BuLi (1.42 M hexane solution, 1.69 mL, 2.4 mmol) in toluene (5 mL) was stirred at −78°C for 1 h, and then to this was added triethyl orthoacrylate (174 mg, 1 mmol). After being stirred for 3 h at room temperature, the mixture was cooled at −78°C. To this was added CuCN (90 mg, 1 mmol), THF (5 mL) and crotyl diethyl phosphate (174 mg, 1.2 mmol) and the whole mixture was stirred for 4 h at room temperature. Extractive work-up (addition of sat. NH_4Cl (aq) and extraction with AcOEt), followed by silica gel column chromatography (hexane:AcOEt, 50:1) gave **3g** (116 mg, 0.74 mmol, 74% yield).

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