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Copper-catalyzed addition reaction of γ,γ-dialkoxyallylic zirconium species with imines

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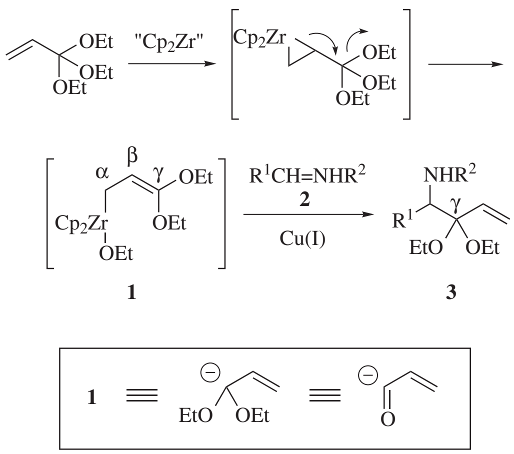
Abstract—In the presence of CuCN, reaction of γ,γ-dialkoxyallylic zirconium species **1** with imines proceeded at the γ-position of **1** to give *gem*-dialkoxyhomoallylic amines **3** in high yield. In this reaction, γ,γ-dialkoxyallylic zirconium species **1** acts as an α,β-unsaturated acyl anion equivalent.

Allylic and substituted allylic metals are invaluable tools for the formation of carbon–carbon bond in organic synthesis.[1] It is well known that allylic organometallics react with imines either at the α-position or at the γ-position to give the corresponding homoallylic amine derivatives, which are important synthetic intermediates.[2] While there are many conventional methods for generating allylic metals, utilization of such allylic metal species having two alkoxyl groups at γ-position has been quite limited mainly due to their low stability.[3] Recently, we have reported that γ,γ-dialkoxyallylic zirconium species **1**, which was found to be thermally stable (at ca. 40 °C) under an argon atmosphere, reacted with carbonyl compounds at the γ-position of zirconium atom to provide the *gem*-dialkoxyhomoallylic alcohol derivatives.[4,5] The acetal moiety in the product can be easily hydrolyzed to carbonyl group, and thus, in this reaction, γ,γ-dialkoxyallylic zirconium species **1** acts as protected acryroyl anion equivalent.[6,7] Under similar conditions, however, this sterically bulky zirconium species **1** did not react with various imines. Moreover, addition of Lewis acid such as $TiCl_4$, TMSOTf, or $BF_3{\cdot}Et_2O$ etc, to activate imine was not fruitful, resulting in a complex mixture in most cases.[8] Further efforts were made to find out an effective additive for addition reaction of **1** to imine on the basis of transmetalation concept. In this letter, we report that in the presence of copper salt, the zirconium species **1** reacted with imines **2** at the γ-position of **1** to give the homoallylic amine derivatives **3** (Scheme 1).

According to our reported procedure, the zirconium species **1** could be easily generated in situ by the reaction of orthoacrylic acid triethyl ester with zirconocene–butene complex[9] ('Cp_2Zr') in toluene at room temperature, through the formation of zirconacyclopropane and the following β-elimination of alkoxyl group (Scheme 1).[4,5,10]



Scheme 1.

Keywords: γ,γ-Dialkoxyallylic zirconium species; Allylation; Copper; Transmetalation; Imine.

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Imines **2** prepared by mixing the corresponding amine and aldehyde in benzene in the presence of anhydrous $MgSO_4$ were used without further purification.

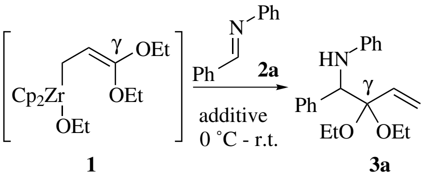
As shown in Table 1, using benzylideneaniline **2a** as a model substrate, the reaction of the zirconium species **1** was conducted, in particular to examine copper salt as an additive, since the zirconium species **1** did not react with **2a** without an additive, resulting in recovery of **2a** (entry 1). Treatment of the zirconium species **1** with 1.0 equiv of CuBr followed by the reaction with **2a** in toluene–THF (1:2) at an ambient temperature gave the *gem*-diethoxyhomoallylamine derivative **3a** in 54% yield (entry 2). Thus, **1** reacted regioselectively at the γ-position. Regarding the solvent effect, while for the generation of the zirconium species **1** toluene was found to be the best, addition of THF was essential for the copper mediated addition reaction. That is, without THF addition reaction in toluene hardly proceeded. The use of a catalytic amount of CuBr (20 mol %) resulted in a similar yield of **3a** (54%) (entry 3). The best result was realized when an equimolar amount of CuCN was used obtaining **3a** in 84% yield (entry 5). Compared to Cu(I) salt, Cu(II) salt such as $CuBr_2$ and $Cu(OTf)_2$ was much less effective (entries 7–10). In particular, the use of stoichiometric amount of Cu(II) salt gave a complex mixture, possibly due to the instability of divalent copper species formed through Zr-to-Cu transmetalation (entries 7 and 9). Thus, in the case of a catalytic amount of Cu(II), divalent copper species formed through Zr-to-Cu transmetalation readily decomposes to Cu(I) and unstable radical species. It should be noted that the control of the reaction temperature is important for efficient reaction. That is, when the reaction temperature warmed up from −78 to 0 °C after the addition of copper salt to a solution of the zirconium species **1**, the color of the reaction mixture turned from yellow to green clear solution. When this green colored solution stood at room temperature, the color gradually changed to dark deep yellow and at the same time black precipitates appeared on the flask wall, indicating the decomposition of copper intermediate formed through Zr-to-Cu transmetalation.[11,12] Therefore, the addition reaction to imines should involve the dialkoxyallylic copper species as a plausible intermediate and the reaction should be carried out at between 0 °C to room temperature within an appropriate reaction period, since below 0 °C reaction rate was extremely slow.

According to the results mentioned above, CuCN-catalyzed reaction of the zirconium species **1** with various imines **2** were examined (Table 2).[13] Not only benzylideneaniline **2a** (entry 1), *p*-substituted arylideneaniline such as *p*-MeO- or *p*-CF_3- derivative gave the addition product **3b** or **3c** in a high yield (entries 2 and 3). Imines derived from aliphatic aldehydes (benzyloxyacetaldehyde and cyclohexane-carbaldehyde) and aromatic amine (aniline) could also be used under similar conditions to give homoallylamine **3d** and **3e** in good yields (entries 4 and 5). With imines derived from aromatic aldehyde (benzaldehyde) and aliphatic amines, the yields of the addition products **3g**–**i** were slightly decreased (entries 7–9). We also examined the reaction with chiral imine derived from benzaldehyde and (*S*)-1-phenylethylamine, which proceeded with good diastereoselectivity (15:1) (entry 9).

Deprotection of diethyl acetal group of **3** could be achieved by simply treating with 50% aqueous solution of trifluoroacetic acid (TFA) in chloroform at 0 °C within 20 min and vinyl ketone **4** was obtained in good yield (Scheme 2).[4] In these reactions shown in this letter, γ,γ-dialkoxyallylic zirconium species **1** acts as either protected or intact acryroyl anion equivalent, whose functionality would be useful for further elaboration to a variety type of compounds.

In conclusion, we have shown that with imines in the presence of CuCN, γ,γ-dialkoxyallylic zirconium species

Table 1. Copper-catalyzed reaction of **1** with benzylideneaniline[a]



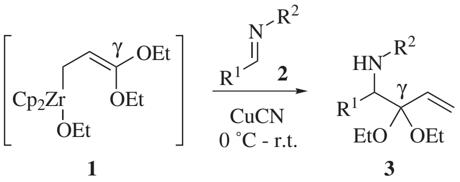
Entry	Additive	Equiv	Yield (%)[b]
1	None		0
2	CuBr	1.0	54
3	CuBr	0.2	54
4	CuBr·Me_2S	1.0	61
5	CuCN	1.0	84
6	CuCN	0.2	58
7	$CuBr_2$	1.0	—[c]
8	$CuBr_2$	0.2	46
9	$Cu(OTf)_2$	1.0	—[c]
10	$Cu(OTf)_2$	0.2	55

[a] Solvent; toluene–THF (2:1).

[b] Isolated yield.

[c] Complex mixture was obtained.

Table 2. CuCN-catalyzed reaction of **1** with imines[a]

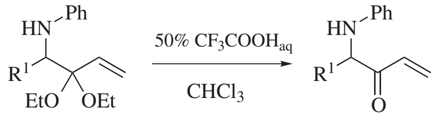


Entry	R^1	R^2		Yield (%)[b]
1	Ph	Ph	**3a**	84
2	*p*-MeOPh	Ph	**3b**	81
3	*p*-CF_3Ph	Ph	**3c**	91
4	$BnOCH_2$	Ph	**3d**	70
5	Cyclohexyl	Ph	**3e**	78
6	Ph	*p*-MeOPh	**3f**	85
7	Ph	Me	**3g**	58
8	Ph	Bn	**3h**	62
9	Ph	(*S*)-1-Phenylethyl	**3i**	64[c]

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

[b] Isolated yield.

[c] Diastereomeric ratio was 15:1.



3a R^1=Ph **4a** 84%
3b R^1=*p*-MeOPh **4b** 81%

Scheme 2.

1 reacts at the γ-position to give the addition product, *gem*-diethoxyhomoallylamine derivatives **3**, which could be easily converted to the vinyl ketone **4**. In this reaction, γ,γ-dialkoxyallylic zirconium species **1** acts as an acryloyl anion equivalent.

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8. We found that in the presence of 1.1 equimolar amount of TMSOTf reaction of benzylideneaniline with **1** in toluene at −78 °C to rt gave *N*-[(2,2-diethoxycyclopropyl)(phenyl)methyl]aniline, which would be formed though the addition of diethoxyketene acetal moiety (reaction at the β-position of **1**) to imine. Similar reaction with carbonyl compounds were already reported. See Ref. 5a.
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13. Typical experimental procedure for the reaction with imine (Table 2, entry 1): 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) and a solution of benzylideneaniline (217 mg, 1.2 mmol) in THF (5 mL) and the whole was stirred for total 8 h at 0 °C at the beginning, then allowing to warm very slowly to room temperature. Extractive work-up followed by silica gel column chromatography (hexane–AcOEt, 10:1) gave *N*-(2,2-diethoxy-1-phenyl-3-butenyl)-aniline **3a** (261 mg, 84% yield).