Triethylborane-Induced Radical Allylation Reaction with Zirconocene–Olefin Complex
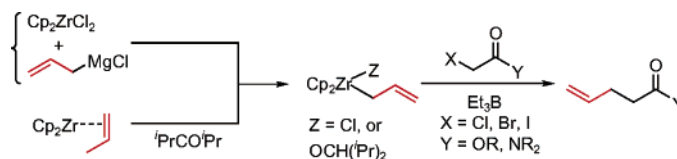
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ABSTRACT

Allylzirconium reagents are effective for radical allylation of α-halo carbonyl compounds. The key steps would be homolytic cleavage of the zirconium–carbon bond and halogen abstraction by the resulting Cp₂ZrCl(III). Zirconocene–olefin complex can be also utilized for the allylation of α-halo compounds.

A radical allylation reaction is synthetically useful because the introduced allyl group serves as a versatile precursor for further functionalization.[1] Recent advances in the radical allylation reaction have mainly benefited from the efficiency of allylstannanes as mediators.[2] The use of tin-based reagents is, however, not always convenient because of the inherent toxicity of organotin derivatives and the difficulty often encountered in removing tin residues from the product.[3] To solve the problems associated with organotin reagents, several alternative approaches have been utilized with some success.[4–6] However, the efficacy of these alternatives often

proved to be inferior to that of allylstannanes. Here we wish to introduce allylzirconium as an allylating reagent via a radical process.[7]

The reagent, allylzirconium, was prepared from Cp₂ZrCl₂ and allylmagnesium chlorides [Method A].[8] Treatment of Cp₂ZrCl₂ (3.0 mmol) with allylmagnesium chloride (3.0 mmol) in THF at −78 °C provided allylzirconium **1**.[9] Benzyl iodoacetate **2a** (1.0 mmol) and Et₃B (0.2 mmol) as a radical initiator were sequentially added, and the mixture was warmed to 25 °C and stirred for 3 h.[10] After aqueous workup,

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(2) (a) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079. (b) Curran, D. P. *Synthesis* **1998**, 417 and 489.

(3) Bagley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072.

(4) Silicon-based radical chain carriers such as allyl tris(trimethylsilyl)-silane are effective alternatives to tin reagents, although these compounds are often costly. (a) Chatgilialoglu, C.; Ballestri, M.; Vecchi, D.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 6383. (b) Chatgilialoglu, C.; Ferreri, C.; Ballestri, M.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 6387. (c) Guindon, Y.; Guerin, B.; Chabot, C.; Oglivie, W. *J. Am. Chem. Soc.* **1996**, *118*, 12528. (d) Porter, N. A.; Wu, J. H.; Zhang, G.; Reed, A. D. *J. Org. Chem.* **1997**, *62*, 6702.

(5) (a) Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **1996**, *118*, 1209. (b) Guyader, F. L.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *J. Am. Chem. Soc.* **1997**, *119*, 7410. (c) Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1998**, *37*, 2864.

(6) Usugi, S.; Yorimitsu, H.; Oshima, K. *Tetrahedron Lett.* **2001**, *42*, 4535.

(7) Recently, we have reported the Cp₂Zr(H)Cl-mediated radical reduction reaction involving homolytic cleavage of the zirconium–hydrogen bond: (a) Fujita, K.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 3137. (b) Fujita, K.; Yorimitsu, H.; Oshima, K. *Synlett* **2002**, 337.

(8) It is known that Cp₂ZrCl₂ reacts with 2-butenylmagnesium chloride to provide a mixture of Cp₂ZrCl(2-butenyl) and Cp₂Zr(2-butenyl)₂. (a) Mashima, K.; Yasuda, H.; Asami, K.; Nakamura, A. *Chem. Lett.* **1983**, 219. We confirmed that Cp₂Zr(2-butenyl)₂, generated by mixing Cp₂ZrCl₂ and 2-butenylmagnesium chloride in a 1:2 ratio, was also effective for the radical allylation. The reactivity of Cp₂Zr(2-butenyl)₂ toward α-halo carbonyl compounds was similar to that of Cp₂ZrCl(2-butenyl).

(9) Use of 1.5 equiv of allylzirconium provided **3a** in only 34% yield along with the recovered α-iodo ester.

(10) (a) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547. (b) Oshima, K.; Utimoto, K. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 40.

Scheme 1. Reaction of Allylic Zirconium Reagent with α-Halo Ester at −78 °C
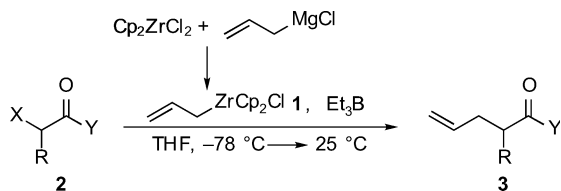
silica gel column purification afforded **3a** in 93% yield (Scheme 1). The representative reactions of various halides with **1** are listed in Table 1. Most of the allylation reactions of α-iodo carbonyl compounds proceeded smoothly to provide the corresponding desired products in satisfactory yields (runs 1−7). It is worth noting that α-bromo esters, usually unreactive for radical allylation reaction, were also efficiently allylated, although an equimolar amount of Et$_3$B was necessary (runs 8−11).[11]

Table 1. Allylation Reaction with Allylzirconium Reagent[a]

| run	substrate	X	Y	R	product	yield
1	**2a**	I	OCH$_2$Ph	H	**3a**	93%
2	**2b**	I	OCH$_2$Ph	CH$_3$	**3b**	77%
3	**2c**	I	−O(CH$_2$)$_3$−		**3c**	90%
4	**2d**	I	O(CH$_2$)$_6$Cl	H	**3d**	77%
5	**2e**	I	O(CH$_2$)$_4$CH=CH$_2$	H	**3e**	81%
6	**2f**	I	NEt$_2$	H	**3f**	96%
7	**2g**	I	N(H)CH$_2$Ph	H	**3g**	82%
8[b]	**2h**	Br	OCH$_2$Ph	H	**3h**	68%
9[b]	**2i**	Br	OEt	$^nC_6H_{13}$	**3i**	88%
10[b]	**2j**	Br	−O(CH$_2$)$_3$−		**3j**	90%
11[b]	**2k**	Br	NEt$_2$	H	**3k**	96%

[a] Cp$_2$ZrCl$_2$ (3.0 mmol), allylmagnesium chlorides (1.0 M THF solution, 3.0 mmol), α-iodo carbonyl compound (1.0 mmol), Et$_3$B (1.0 M hexane solution, 0.2 mmol), −78 °C, 5 h. [b] Cp$_2$ZrCl$_2$ (3.0 mmol), allylmagnesium chlorides (1.0 M THF solution, 3.0 mmol), α-bromo carbonyl compound (1.0 mmol), Et$_3$B (1.0 M hexane solution, 1.0 mmol), −78 °C, 5 h.

In the absence of Et$_3$B, only a trace amount of allylation products was observed. Furthermore, the addition of a radical scavenger, 2,2,6,6-tetramethylpiperidine-*N*-oxyl, suppressed the reaction and yielded only a trace amount of desired product **3**. On the basis of these findings, we propose a radical mechanism for this new allylation reaction (Scheme 2). An ethyl radical, generated from Et$_3$B by the action of a trace amount of oxygen, abstracts iodide homolytically from α-iodo ester to afford the carbon-centered radical **4**. The radical **4** adds to allylzirconium **1** to provide **5**, which collapses to the allylation product **3a** and liberates a zirconium(III) species **6**. The latter then abstracts iodide from α-iodo ester, regenerating the alkyl radical **4**.

Encouraged by these results, we next investigated an intermolecular three-component coupling reaction of allylzir-

(11) With a catalytic amount (0.20 equiv) of Et$_3$B, most of the α-bromo ester was recovered along with a trace of the allylation product.

Scheme 2. Plausible Mechanism
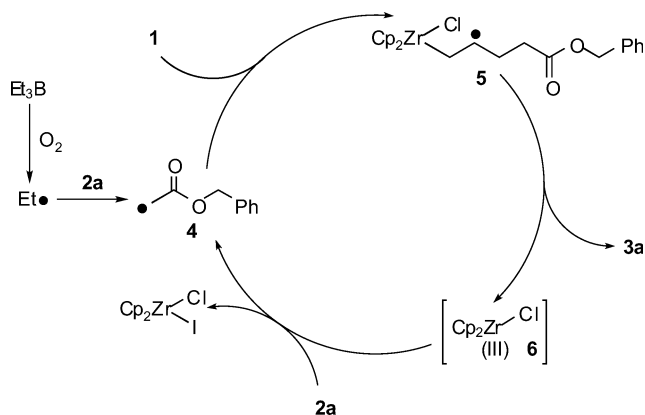
coniums, alkyl halides, and alkenes. A sequential addition of cyclohexyl iodide (5.0 mmol), *tert*-butyl acrylate (1.0 mmol), and Et$_3$B (0.2 mmol) to a solution of allylzirconium (**1**, 3.0 mmol) in THF afforded the coupling product **7a** in 84% yield (Scheme 3). In this case, a cyclohexyl radical adds

**Scheme 3.** Three-Component Coupling Reaction
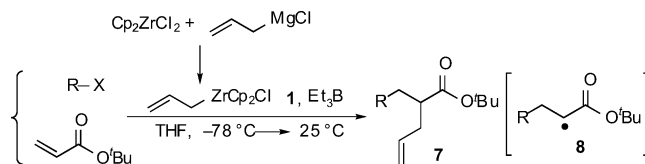
to the terminal carbon of acrylate yielding radical intermediate **8**. The coupling product **7** is formed by the radical allylation of **8** with **1**. The use of isopropyl iodide in place of cyclohexyl iodide also furnished the corresponding adduct **7b** in good yield (Table 2). Alkyl bromide also underwent three-component coupling reaction upon treatment of allylzirconium **1**.

Table 2. Intermolecular Three-Component Coupling Reaction[a]

run	R	product	yield
1	$^cC_6H_{11}I$	**7a**	84%
2	^iPrI	**7b**	70%
3[b]	$^cC_6H_{11}Br$	**7a**	29%
4[b]	^iPrBr	**7b**	50%

[a] Cp$_2$ZrCl$_2$ (3.0 mmol), allylmagnesium chlorides (1.0 M THF solution, 3.0 mmol), alkyl halide (5.0 mmol), *tert*-butyl acrylate (1.0 mmol), Et$_3$B (1.0 M hexane solution, 0.2 mmol), −78 °C, 5 h. [b] Cp$_2$ZrCl$_2$ (3.0 mmol), allylmagnesium chlorides (1.0 M THF solution, 3.0 mmol), alkyl halide (5.0 mmol), *tert*-butyl acrylate (1.0 mmol), Et$_3$B (1.0 M hexane solution, 1.0 mmol), −78 °C, 5 h.

Recently, we have reported that zirconocene−olefin complex can be utilized for allylation of carbonyl compounds.[12] This result encouraged us to try the present radical

Scheme 4. Allylation Reaction with Zirconium−Olefin Complex

Scheme 4. Allylation Reaction with Zirconium−Olefin Complex

Scheme 5. Crotylation Reaction with Zirconium−Olefin Complex
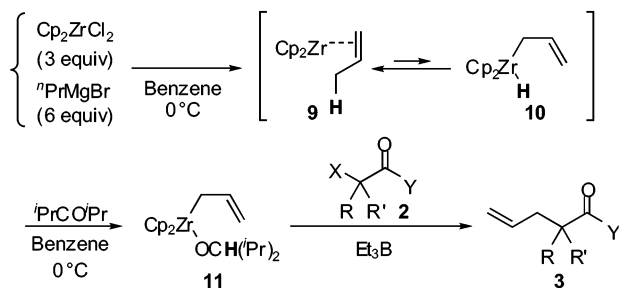
allylation process using this reagent [Method B] (Scheme 4). A zirconocene−1-propene complex, derived from Cp$_2$-ZrCl$_2$ (3.0 mmol) and propylmagnesium bromide (6.0 mmol), reacts with diisopropyl ketone (4.5 mmol) to afford **11**. The addition of benzyl iodoacetate **2a** (1.0 mmol) in the presence of Et$_3$B (0.2 mmol) provided the desired adduct **3a** in excellent yield. The reactions with other α-carbonyl compounds are summarized in Table 3. This protocol is also

Table 3. Allylation Reaction with Zirconium−Olefin Complex[a]

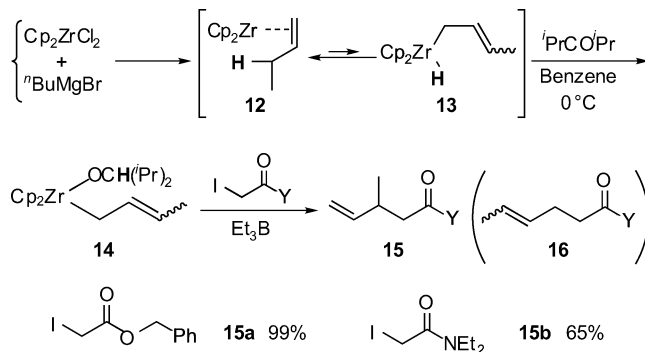| run	2	X	Y	R	R′	3	yield
1	**2a**	I	OCH$_2$Ph	H	H	**3a**	93%
2	**2b**	I	OCH$_2$Ph	CH$_3$	H	**3b**	55%
3[b]	**2i**	Br	OEt	^{n}C$_6$H$_{13}$	H	**3i**	72%
4[b]	**2l**	Br	O−^{n}C$_7$H$_{15}$	CH$_3$	CH$_3$	**3l**	78%
5[b]	**2m**	Cl	OCH$_2$Ph	CH$_3$	H	**3m**	56%

[a] Cp$_2$ZrCl$_2$ (3.0 mmol), Grignard reagent (1.0 M THF solution, 6.0 mmol), diisopropyl ketone (4.5 mmol), α-iodo carbonyl compound (1.0 mmol), Et$_3$B (1.0 M hexane solution, 0.2 mmol), −78 °C, 5 h. [b] Cp$_2$ZrCl$_2$ (3.0 mmol), Grignard reagent (1.0 M THF solution, 6.0 mmol), diisopropyl ketone (4.5 mmol), α-halo carbonyl compound (1.0 mmol), Et$_3$B (1.0 M hexane solution, 1.0 mmol), −78 °C, 5 h.

general and can be applied to a broad range of α-halo carbonyl compounds. It is worth noting that α-chloro carbonyl compounds and tertiary bromides can be allylated in good yields.[13]

Moreover, the reaction also works for various allylic zirconiums. Treatment of crotylzirconium **14**, derived from

Cp$_2$ZrCl$_2$, butylmagnesium bromide, and diisopropyl ketone with benzyl iodoacetate **2a** afforded benzyl 3-methyl-4-pentenoate **15a** in 99% yield with high regioselectivity (Scheme 5). The regioisomer, benzyl 4-hexenoate **16**, was not detected in the reaction mixture. This reaction is particularly useful because radical-trapping with crotylstannanes has generally resulted in failure.[14] In contrast, the crotylzirconium reagent afforded the desired products satisfactorily in terms of both yields and selectivities. α-Iodo amide also yielded the corresponding γ-adduct exclusively in excellent yields.

In conclusion, we have found that allylzirconium species could be utilized for a radical allylation process as an excellent alternative to allyltributyltin. The key steps would be homolytic cleavage of the zirconium−carbon bond and halogen abstraction by Cp$_2$ZrCl(III). The present protocol circumvents the drawback of organotin compounds and provides us with a useful synthetic method for the construction of carbon skeletons via a radical process.

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

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(12) (a) Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 12115. (b) Fujita, K.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2003**, 42, 2550. (c) Fujita, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* Submitted for publication.
(13) In general, the radical allylation of tertiary bromides provides the desired products in poor yields due to the steric effect.
(14) Failure of reaction with crotylstannane can be attributed to the reduced reactivity of crotylstannane and the isomerization to more reactive 3-buten-2-ylstannane. (a) Clive, D. L. J.; Psul, C. C.; Wang, Z. *J. Org. Chem.* **1997**, *62*, 7028. Sibi has developed selective crotylation of α-carbonyl radicals at low temperatures with a Lewis acid catalyst. (b) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9427. (c) Sibi, M. P.; Miyabe, H. *Org. Lett.* **2002**, *4*, 3435.