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Triethylborane-Induced Radical Allylation Reaction with Zirconocene–Olefin Complex

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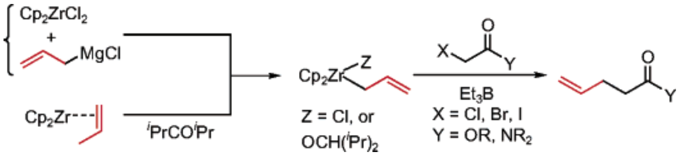
ABSTRACT



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 $Cp_2ZrCl(III)$. 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 Cp_2ZrCl_2 and allylmagnesium chlorides [Method A].[8] Treatment of Cp_2ZrCl_2 (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 Et_3B (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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[1] (a) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001. (b) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

[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 $Cp_2Zr(H)Cl$-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.

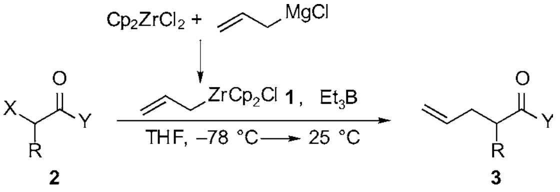
[8] It is known that Cp_2ZrCl_2 reacts with 2-butenylmagnesium chloride to provide a mixture of Cp_2ZrCl(2-butenyl) and Cp_2Zr(2-butenyl)$_2$. (a) Mashima, K.; Yasuda, H.; Asami, K.; Nakamura, A. *Chem. Lett.* **1983**, 219. We confirmed that Cp_2Zr(2-butenyl)$_2$, generated by mixing Cp_2ZrCl_2 and 2-butenylmagnesium chloride in a 1:2 ratio, was also effective for the radical allylation. The reactivity of Cp_2Zr(2-butenyl)$_2$ toward α-halo carbonyl compounds was similar to that of Cp_2ZrCl(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.

10.1021/ol036431e CCC: $27.50

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_3B was necessary (runs 8−11).[11]

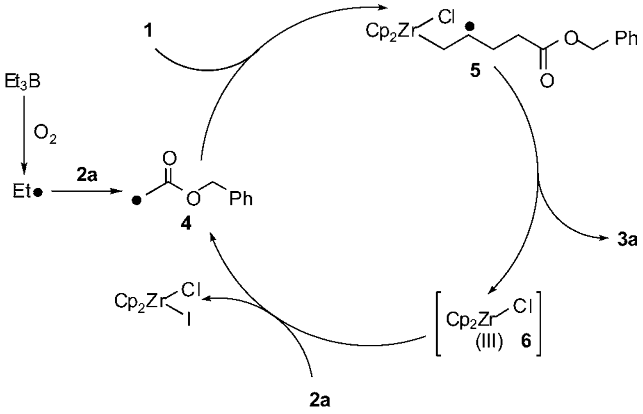
Table 1. Allylation Reaction with Allylzirconium Reagent[a]

run	substrate	X	Y	R	product	yield
1	**2a**	I	OCH_2Ph	H	**3a**	93%
2	**2b**	I	OCH_2Ph	CH_3	**3b**	77%
3	**2c**	I	$-O(CH_2)_3-$		**3c**	90%
4	**2d**	I	$O(CH_2)_6Cl$	H	**3d**	77%
5	**2e**	I	$O(CH_2)_4CH{=}CH_2$	H	**3e**	81%
6	**2f**	I	NEt_2	H	**3f**	96%
7	**2g**	I	$N(H)CH_2Ph$	H	**3g**	82%
8[b]	**2h**	Br	OCH_2Ph	H	**3h**	68%
9[b]	**2i**	Br	OEt	$^{n}C_6H_{13}$	**3i**	88%
10[b]	**2j**	Br	$-O(CH_2)_3-$		**3j**	90%
11[b]	**2k**	Br	NEt_2	H	**3k**	96%

[a] Cp_2ZrCl_2 (3.0 mmol), allylmagnesium chlorides (1.0 M THF solution, 3.0 mmol), α-iodo carbonyl compound (1.0 mmol), Et_3B (1.0 M hexane solution, 0.2 mmol), −78 °C, 5 h. [b] Cp_2ZrCl_2 (3.0 mmol), allylmagnesium chlorides (1.0 M THF solution, 3.0 mmol), α-bromo carbonyl compound (1.0 mmol), Et_3B (1.0 M hexane solution, 1.0 mmol), −78 °C, 5 h.

In the absence of Et_3B, 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_3B 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**.

Scheme 2. Plausible Mechanism



Encouraged by these results, we next investigated an intermolecular three-component coupling reaction of allylzirconiums, alkyl halides, and alkenes. A sequential addition of cyclohexyl iodide (5.0 mmol), *tert*-butyl acrylate (1.0 mmol), and Et_3B (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 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**.

Scheme 3. Three-Component Coupling Reaction

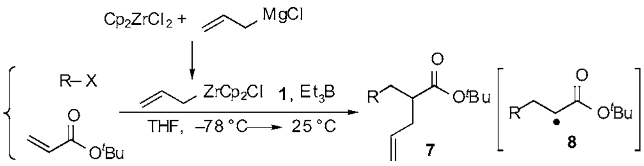


Table 2. Intermolecular Three-Component Coupling Reaction[a]

run	R	product	yield
1	$^{c}C_6H_{11}I$	**7a**	84%
2	^{i}PrI	**7b**	70%
3[b]	$^{c}C_6H_{11}Br$	**7a**	29%
4[b]	$^{i}PrBr$	**7b**	50%

[a] Cp_2ZrCl_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_3B (1.0 M hexane solution, 0.2 mmol), −78 °C, 5 h. [b] Cp_2ZrCl_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_3B (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

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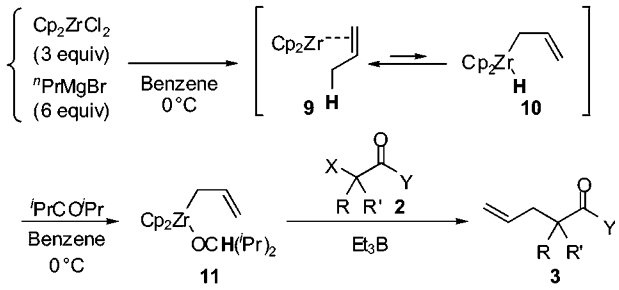
[11] With a catalytic amount (0.20 equiv) of Et_3B, most of the α-bromo ester was recovered along with a trace of the allylation product.

Scheme 4. Allylation Reaction with Zirconium−Olefin Complex



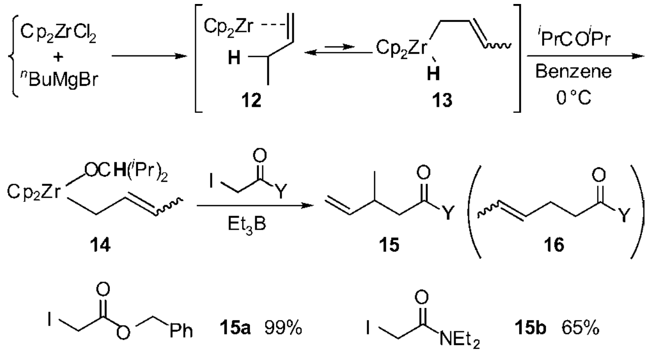
allylation process using this reagent [Method B] (Scheme 4). A zirconocene−1-propene complex, derived from Cp_2ZrCl_2 (3.0 mmol) and propylmagnesium bromide (6.0 mmol), reacts with diisopropyl ketone (4.5 mmol) to afford **11**. The addition of benzyl iodoacetate **2a** (1.0 mmol) in the presence of Et_3B (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 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]

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

run	2	X	Y	R	R′	3	yield
1	**2a**	I	OCH_2Ph	H	H	**3a**	93%
2	**2b**	I	OCH_2Ph	CH_3	H	**3b**	55%
3[b]	**2i**	Br	OEt	$^nC_6H_{13}$	H	**3i**	72%
4[b]	**2l**	Br	$O{-}^nC_7H_{15}$	CH_3	CH_3	**3l**	78%
5[b]	**2m**	Cl	OCH_2Ph	CH_3	H	**3m**	56%

[a] Cp_2ZrCl_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_3B (1.0 M hexane solution, 0.2 mmol), −78 °C, 5 h. [b] Cp_2ZrCl_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_3B (1.0 M hexane solution, 1.0 mmol), −78 °C, 5 h.

Scheme 5. Crotylation Reaction with Zirconium−Olefin Complex



Moreover, the reaction also works for various allylic zirconiums. Treatment of crotylzirconium **14**, derived from Cp_2ZrCl_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 $Cp_2ZrCl(III)$. 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.

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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.