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Copper-catalyzed allylations of *o*-vinylbenzylzirconocene intermediate

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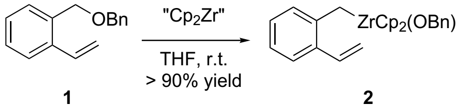
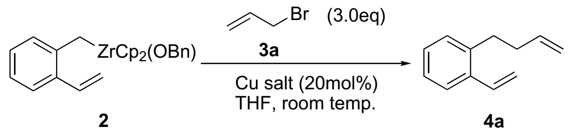
Abstract—Benzylzirconocene intermediate, which was readily prepared by the reaction of *o*-alkoxymethylstyrene with 'Cp_2Zr' under mild conditions, reacted with allylic halides or phosphates in the presence of catalytic amount of CuCl to give allylated products in good yields.

Alkenyl- and alkylzirconocene species involving allylzirconocene species prepared by hydrozirconation with corresponding alkyne/alkene or reactions of allyl ether derivatives with 'Cp_2Zr' (zirconocene–butene complex; zirconocene equivalent) are widely used in organic synthesis.[1] In contrast, benzylic-type zirconocene species are rarely applied to organic synthesis.[2] In general, benzylic metal species that contains *o*-vinyl substituent would be useful intermediate as it is a reactive benzyl metal attached with a reactive and convertible styrene–olefin unit. To the best of our knowledge, however, only a few examples[3] of *o*-vinylbenzyl metal species are known because of the difficulty in their preparation due to the high reactivity of the styrene–olefin unit.

We have reported on a generation of *o*-vinylbenzylzirconocene intermediate **2** by the reaction of *o*-benzyloxymethylstyrene **1** with 'Cp_2Zr' in good yield under mild conditions (Scheme 1).[4,5] Preparation of **2** by transmetalation procedure would be difficult because of the reason described above.



Scheme 1.



Scheme 2.

For the purpose of synthetic use of **2**, allylation,[6] which is the one of the most useful C–C bond forming reactions, was examined, and the results of the copper-catalyzed effective allylations of **2** with allylic halides or phosphates are described in this letter.

It is known that alkylzirconocene species react with allylic halides or phosphates to give allylated products in the presence of catalytic amount of CuCN.[6a] Thus, various copper salts for the reaction of **2** with allyl bromide **3a** were examined (Scheme 2), and the results are summarized in Table 1.

Although the reaction did not proceed without a copper catalyst (entry 1), most of the copper salts investigated showed catalytic activity (entries 2–8). Not only Cu(I) salt, but Cu(II) salt also catalyzed the reaction to give an allylated product in moderate yield (entry 6).

Based on the results shown in Table 1, we examined the optimal conditions for the reaction of **2** with **3a** in the presence of a CuCl catalyst (Table 2). All reactions were carried out by using **2** (1.0 equiv), **3a** (1.5 or 3.0 equiv) and CuCl catalysts (5, 10 or 20 mol %) in THF. It is

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Keywords: Benzylzirconocene; Styrene; Allylation.

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Table 1. Investigation for copper salts[a]

Entry	Cu salts (20 mol%)	Yield (%)[b]
1	None	No reaction
2	CuCl	77
3	CuBr	55
4	CuBr–SMe$_2$	67
5	CuI	56
6	CuBr$_2$	47
7	CuCN	34
8	CuCN–2LiCl	33

[a] The reaction of **2** (0.1 mmol) with **3a** (0.3 mmol) was carried out in the presence of Cu salt (0.02 mmol) in THF (1 mL) at room temperature for 5 h.
[b] HPLC yields.

Table 2. Optimization of reaction conditions of **2** with **3a** in the presence of CuCl[a]

Entry	CuCl (mol%)	**3a** (equiv)	**4a** Yield (%)[b]
1	20	3.0	77[c]
2	20	3.0	95
3	20	1.5	95
4	10	1.5	95 (88)
5	5	1.5	90

[a] Unless otherwise noted, the reaction of **2** (0.1 mmol) with **3a** (0.15 or 0.3 mmol) was carried out in the presence of CuCl (5–20 μmol) in THF (1 mL) at reflux for 5 h.
[b] HPLC yields. Isolated yield was shown in parentheses.
[c] Reaction was carried out at room temperature.

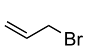
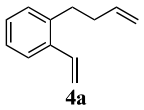
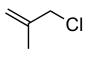
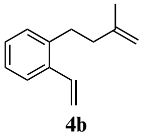
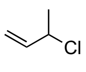
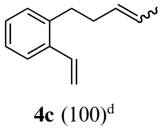
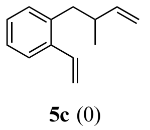
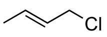
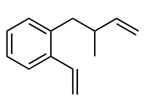
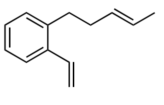
essential to heat the reaction mixture to reflux to bring about an efficient formation of **4a** (entries 1 and 2).

At a reduction of the amount of **3a** (1.5 equiv) or CuCl (10 mol%), no significant change was observed (entries 3 and 4). Further reduction of CuCl (5 mol%), however, reduced the product yield slightly (entry 5). It can thus be considered that the reaction conditions described in entry 4 in Table 2 would be optimal. The scope and limitations of the present allylation of **2** are shown in Tables 3 and 4.

A variety of allylic halides or phosphates could be used in the present allylation,[7] and allylic chlorides, bromides and phosphates all reacted in similar efficiency. Symmetrical allylic halide, such as allyl bromide **3a** and methallyl chloride **3b**, gave the corresponding allylated products **4a**[8] and **4b** in good yields (Table 3, entries 1 and 2). Allylation with unsymmetrical allylic halide **3c** or **3d** gave S_N2' product (**4c** or **4d**) as a sole or major product ($S_N2/S_N2' = 9/91$) (entries 3 and 4). In the reaction of prenyl bromide **3e**, which is sterically bulky at γ-position, S_N2 product **5e** was obtained as a major product ($S_N2/S_N2' = 69/31$) (Table 4, entry 1). Lipshutz and co-workers reported[6a] that S_N2' product was formed predominantly in the copper-catalyzed allylation of alkylzirconocene derivatives with prenyl bromide. Thus, the present copper-catalyzed reaction of **2** would suggest that the steric effect is decisive for the regio-selectivity. Phosphate **3f** prepared from cinnamyl alcohol reacted with **2** also gave allylated products in good yield with similar S_N2' selectivity (entry 2). The reaction of **2** with propargyl bromide **3g** produced allene derivative **4g** as a sole product, and acetylene derivative **5g** was not detected at all (entry 3). 1,3-Diene derivatives **4h** could be obtained in a moderate yield as a mixture of E/Z isomers ($E/Z = 2.4/1$) along with 1,4-diene compound **5h** by the reaction of phosphate **3h** (entry 4).

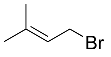
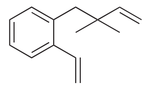
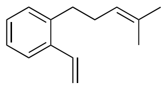
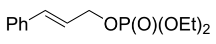
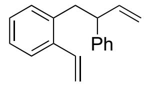
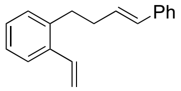
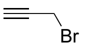
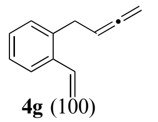
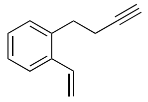
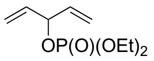
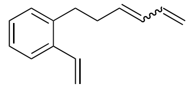
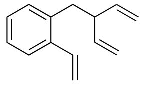
As a synthetic application of allylated product,[9] intramolecular Diels–Alder reaction of diene **4h** was carried

Table 3. CuCl-catalyzed allylation of benzylzirconocene intermediate **2**[a] with allyl- or mono-methylated allyl halides

Entry	Halide/phosphate	Product(s)[b]		Yield (%)[c]
		S_N2'	S_N2	
1	 **3a**	 **4a**		88
2	 **3b**	 **4b**		87
3	 **3c**	 **4c** (100)[d]	 **5c** (0)	87
4	 **3d**	 **4d** (91)	 **5d** (9)	87

[a] Unless otherwise noted, the reaction of **2** (1 mmol) with halide/phosphate **3a–h** (1.5 mmol) was carried out in the presence of CuCl (0.1 mmol) in THF (10 mL) at reflux temperature for 5 h.
[b] Ratios of S_N2' and S_N2 were determined by ^{1}H NMR and are shown in parentheses.
[c] Isolated yields.
[d] Ratio was determined by ^{1}H NMR as major/minor = 2.8/1. Geometry was not determined.

Table 4. CuCl-catalyzed allylation of benzylzirconocene intermediate **2**[a] with allyl-related halides or phosphates

Entry	Halide/phosphate	Product(s)[b]		Yield (%)[c]
		S_N2'	S_N2	
1	 **3e**	 **4e** (31)	 **5e** (69)	92
2	 **3f**	 **4f** (92)	 **5f** (8)	86
3	 **3g**	 **4g** (100)	 **5g** (0)	84
4[d]	 **3h**	 **4h** (78)[e]	 **5h** (22)	75

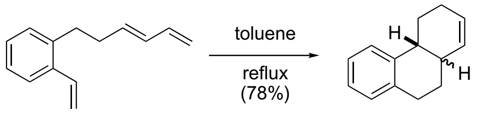
[a] Unless otherwise noted, the reaction of **2** (1 mmol) with halide/phosphate **3a–h** (1.5 mmol) was carried out in the presence of CuCl (0.1 mmol) in THF (10 mL) at reflux temperature for 5 h.

[b] Ratios of S_N2' and S_N2 were determined by ^1H NMR and are shown in parentheses.

[c] Isolated yields.

[d] Phosphate (2 equiv), which was prepared in situ, was used.

[e] Ratio was determined by ^1H NMR as $E/Z = 2.4/1$.



(E)-**4h**

6
cis/trans =1.7/1

Scheme 3.

out in toluene under reflux temperature. It should be mentioned that only (*E*)-**4h** was consumed to give a *cis/trans* mixture of tricyclic products **6**[10] in a 1.7/1 ratio in 76% yield (Scheme 3). On the other hands, (*Z*)-**4h** was recovered in a quantitative yield under the same conditions.

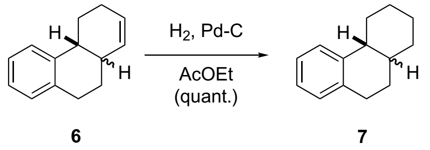
In conclusion, we found an effective allylation of benzylzirconocene intermediate **2** with various allylic halides or phosphates. A wide variety of 2-(3′-alkenyl)-styrene derivatives can be synthesized by this protocol. Studies of the reactions of **2** with more functionalized allylic halides or phosphates and synthetic applications of the allylated products are now in progress.

References and notes

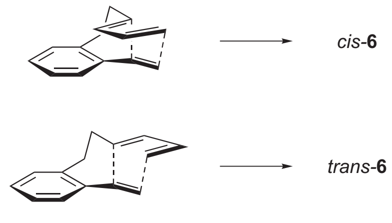
1. For a recent reviews, (a) *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Germany, 2002; (b) Recent advances in the chemistry of zirconocenes, Suzuki, K.; Wipf, P. Eds.; Symposium-in print *Tetrahedron* **2004**, *60*, 1267; (c) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853, and references cited therein.
2. Although hydrozirconation of 1-phenyl-1-propene and its related compounds gave benzylic zirconocene species, the regio-selectivity and yield were not satisfactory; Gibson, T. *Organometallics* **1987**, *6*, 918.
3. To the best of our knowledge, Li species is not known. Although corresponding Mg species are known in several examples, most of synthetic applications of 2-vinylbenzyl magnesium species are limited to polymer chemistry. (a) Hatada, K.; Shiozaki, T.; Ute, K.; Kitayama, T. *Polymer Bull.* **1988**, *19*, 231; (b) Kuendig, E. P.; Perret, C. *Helv. Chim. Acta* **1981**, *64*, 2606; (c) Duboudin, J. G.; Jousseaume, B.; Pinet, M. *J. Chem. Soc., Chem. Commun.* **1977**, 454.
4. Hanzawa, Y.; Ikeuchi, Y.; Nakamura, T.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 6503.
5. ‘Cp_2Zr’-Catalyzed alkylation of styrene–olefin has been reported. (a) Cesati, R. C.; Armas, J.; Hoveyda, A. H. *Org. Lett.* **2002**, *4*, 395; (b) Armas, J.; Hoveyda, A. H. *Org. Lett.* **2001**, *3*, 2097; (c) Armas, J.; Kolis, S. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 5977; (d) Terao, J.; Torii, K.; Saito, K.; Kambe, N.; Baba, A.; Sonoda, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 2653; (e) Terao, J.; Watanabe, T.; Saito, K.; Kambe, N.; Sonoda, N. *Tetrahedron Lett.* **1998**, *39*, 9201; (f) Swanson, D. R.; Rousset, C. J.; Negishi, E.; Takahashi, T.; Seki, T.; Saburi, M.; Uchida, Y. *J. Org. Chem.* **1989**, *54*, 3521.
6. Organozirconium-mediated allylation for (a) Venanzi, L. M.; Lehmann, R.; Keil, R.; Lipshutz, B. H. *Tetrahedron Lett.* **1992**, *33*, 5857; (b) Heron, N. M.; Adams, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 6205; (c) Takahashi, T.; Kotora, M.; Kasai, K.; Suzuki, N. *Organometallics* **1994**, *13*, 4183.
7. Typical experimental procedure: A mixture of **1** (1 mmol) and $Cp_2Zr(n\text{-}Bu)_2$, which was generated by the addition of *n*-BuLi (2 equiv) to Cp_2ZrCl_2 in THF (5 mL) at −78 °C, was gradually warmed to room temperature and the mixture was stirred for 3 h. To this solution, **3a** (1.5 equiv) in THF (2 mL) and CuCl (10 mol%) were added and refluxed for 5 h. After cooling to room temperature, 1 N HCl was added and extracted with ether. The organic layer was washed with brine, dried over anhydrous $MgSO_4$

and the filtrate was concentrated to dryness. The residue was purified by flash chromatography (*n*-hexane), and further purification was carried out by MPLC (*n*-hexane) to give **4a**[8] in 88% yield.

8. Padwa, A.; Ku, A. *J. Am. Chem. Soc.* **1978**, *100*, 2181.
9. Synthetic applications of 2-(3′-alkenyl)-styrene derivatives are studied vigorously by Taylor et al. (a) Bird, A. J.; Taylor, R. J. K.; Wei, X. *Synlett* **1995**, 1237; (b) Wei, X.; Taylor, R. J. K. *Tetrahedron Lett.* **1997**, *38*, 6467; (c) Wei, X.; Taylor, R. J. K. *Tetrahedron: Asymmetry* **1997**, *8*, 665; (d) Wei, X.; Taylor, R. J. K. *Tetrahedron Lett.* **1996**, *37*, 4209; (e) Wei, X.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **1996**, 187.
10. The structure and stereochemistry of **6** were determined by transformation (reduction of C═C double bond under the H_2/Pd–C in AcOEt) to known compounds **7**,[11] and ratio was determined by GC.



In molecular model study of possible transition states for the intramolecular Diels–Alder reaction of (*E*)- or (*Z*)-**4h**, two *exo*- and *endo*-transition states derived from (*E*)-**4h** showed feasible transition states (see below). On the contrary, (*Z*)-**4h** forms sterically and conformationally reluctant transition states. A detailed discussion will be reported in due course.



11. Bansal, R. C.; Browne, C. E.; Eisenbraun, E. J. *J. Org. Chem.* **1988**, *53*, 452.