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Copper-Catalyzed Allylations of Zirconocene Intermediates Generated from *o*-Alkenyl or *o*-Alkynylbenzyl Ether Derivatives and Zirconocene−Butene Complex

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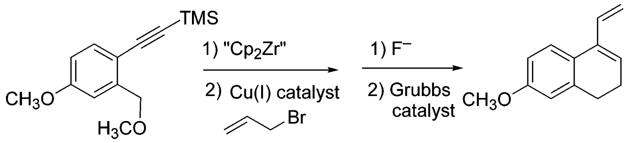

o-Alkenyl or alkynyl benzylzirconocene intermediate, which was readily generated by the reaction of 2-alkoxymethylstyrene or 2-alkoxymethyl-1-(trimethylsilylethynyl)-benzene derivative with zirconocene−butene complex (Negishi reagent, "Cp$_2$Zr"), reacted with allyl or propargyl halides in the presence of a catalytic amount of CuCl to give allylation or allenylation products. Conversion to Dane's diene, which is a key intermediate for estrone synthesis, was efficiently carried out by enyne olefin metathesis of the allylation products.

Alkyl- or alkenylzirconocene chlorides are easily accessible by hydrozirconation of unsaturated compounds with Schwartz reagent (Cp$_2$Zr(H)Cl, Cp = cyclopentadienyl) with high regio- and stereoselectivity. The nucleophilic reactivity of organozirconocene chloride complexes, however, is very poor, and the addition to aldehydes, for example, scarcely takes place. To increase the reactivity of the organozirconocene chloride complexes, activation procedures by adding a stoichiometric or catalytic additive have been devised, and thus organozirconocene chloride complexes have come to be recognized as mild and versatile nucleophilic organometallics.[1] On the other hand, it is impossible to generate benzylzirconocene species through hydrozirconation. Transmetalation from benzylmetal (BnM, M = MgBr or Li) compounds to zirconocene complex could be a suitable way to prepare benzylic zirconocene species. To the best of our knowledge, however, a few reported examples[2] of *o*-vinylbenzylmetal species are known to be equilibrated with benzocyclobutane compound because of the presence of the highly reactive styrene-olefin unit. Recently, we reported on the generation of *o*-vinylbenzylzirconocene intermediate **2** (Scheme 1)[3] by the reaction of *o*-benzyloxymethylstyrene (**1a**) and a stoichiometric amount of zirconocene−butene complex (Negishi reagent, "Cp$_2$Zr") and its copper-catalyzed acylations[4,5] and allylations[6,7] (Scheme 2). It is worth noting that the "Cp$_2$Zr"-mediated pair selective dimerization of the styrene double bond is a well-established process.[8]

In this paper, we report on (1) allylations of 2-vinyl- or 2-(TMS-ethynyl)-1-benzylzirconocene intermediates with various allyl halides and (2) the transformation of allylation products to Dane's diene, which is an important intermediate for the preparation of estrone, through intramolecular enyne metathesis using Grubbs catalyst.

At the outset, *o*-vinylbenzylzirconocene intermediate **2**, which was generated from *o*-benzyloxymethylstyrene (**1a**) with "Cp$_2$Zr" in THF at ambient temperature, was treated with allyl bromide (**3a**) in THF in the presence of a catalytic amount (10 mol %) of CuCl at reflux temperature to give the corresponding allylation product **4a** in 88% yield (Table 1, entry 1). Under the same conditions, *p*-methoxystyrene derivative **1b** and *p*-fluorostyrene derivative **1c** gave allylation products **4b** and **4c**, respectively, in good yields (entries 2 and 3). Thus, the electronic nature of a para substituent has little effect on the reactivity of styrene olefin in the ligand exchange with "Cp$_2$Zr". C$_2$-Halogenated allylic halides were also used under the present allylation conditions, and thus the corresponding vinyl halide derivatives **4d** and **4e** were obtained in moderate to good yields (entries 4 and 5). An ester group was tolerated in the present reaction, and the reaction of **3d** gave the corresponding allylation product **4f** as the sole product in 88% yield (entry 6). It is noteworthy that the conjugate addition did not take place in the reaction of **3d**, which possesses the Michael acceptor unit. In the reaction of **1a** with propargyl bromide (**3e**), allene derivative **4g** was obtained as the sole product, and the acetylene derivative was not detected at all (entry 7). Thus, the reaction with prop-

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(1) For recent reviews: (a) Marek, I., Ed. *Titanium and Zirconium in Organic Synthesis*; Wiley-VCH: Germany, 2002 (b) Suzuki, K., Wipf, P., Eds. Recent Advances in the Chemistry of Zirconocenes. In Symposium-in Print. *Tetrahedron* **2004**, *60*, 1267. (c) Wipf, P.; Jahn, H., *Tetrahedron* **1996**, *52*, 12853 and references cited therein.

(2) To the best of our knowledge, the Li species is unknown. Although corresponding Mg species are known in several examples, the use of 2-vinylbenzylmagnesium species has been limited mostly 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.

(3) Hanzawa, Y.; Ikeuchi, Y.; Nakamura, T.; Taguchi, T. *Tetrahedron Lett.***1995**, *36*, 6503.

(4) Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.***2004**, *45*, 4495.

(5) Organozirconium-mediated acylations, see: (a) Wipf, P.; Xu, W. *Synlett* **1992**, 718. (b) Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115.

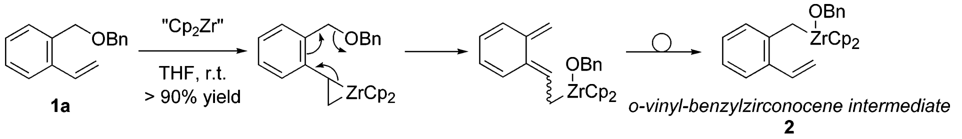
(6) Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **2004**, *45*, 3717.

(7) Organozirconium-mediated allylations, see.: (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.

(8) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124 and references cited therein.

10.1021/jo048860b CCC: $30.25

SCHEME 1. Generation of Benzylzirconocene Intermediate 2



SCHEME 2. Acylations and Allylations of Benzylzirconocene Intermediate 2

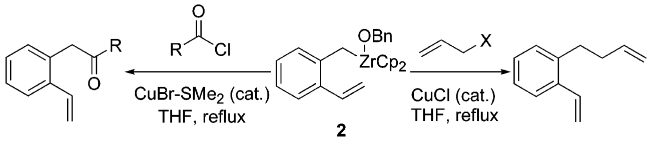
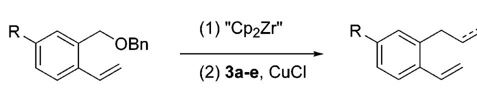
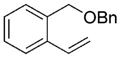
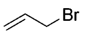
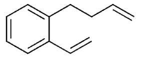
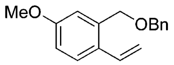
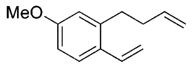
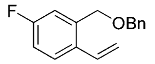
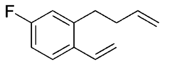
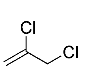
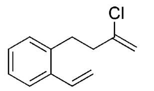
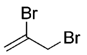
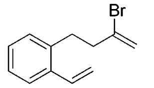
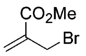
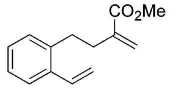
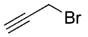
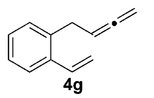


TABLE 1. CuCl-Catalyzed Allylations of 2-Alkoxymethylstyrene Derivatives[a]

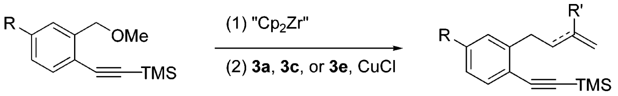


1a-c → **4a-g**

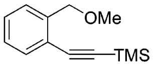
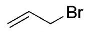
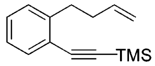
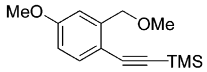
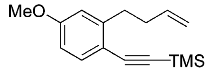
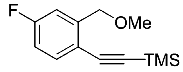
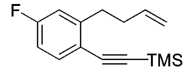
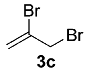
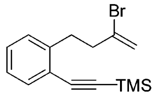
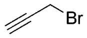
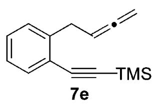
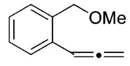
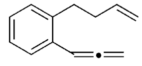
entry	1a-c	3a-e	4a-g	yield (%)[b]
1	 **1a**	 **3a**	 **4a**	88
2	 **1b**	**3a**	 **4b**	83
3	 **1c**	**3a**	 **4c**	62
4	**1a**	 **3b**	 **4d**	56
5	**1a**	 **3c**	 **4e**	80
6	**1a**	 **3d**	 **4f**	88
7	**1a**	 **3e**	 **4g**	84[c]

[a] Reaction conditions: (1) **1a**−**c** (0.5 mmol), "Cp_2Zr" (0.525 mmol), THF (7 mL), rt; (2) **3a**−**e** (0.75 mmol), CuCl (0.05 mmol), THF, reflux. [b] Isolated yields. [c] Acetylene derivative (S_N2 product) was not detected by 300 MHz ^1H NMR.

TABLE 2. CuCl-Catalyzed Allylations of 2-Alkoxymethyl-1-(TMS-ethynyl)-benzene Derivatives[a]



5a-c → **7a-e**

entry	5a-c or 6	3a, 3c, or 3e	7a-e or 8	yield (%)[b]
1	 **5a**	 **3a**	 **7a**	80
2	 **5b**	**3a**	 **7b**	90
3	 **5c**	**3a**	 **7c**	89
4	**5a**	 **3c**	 **7d**	78
5	**5a**	 **3e**	 **7e**	68[c]
6	 **6**	**3a**	 **8**	complex mixture

[a] Reaction conditions: (1) **5a**−**c** or **6** (0.5 mmol), "Cp_2Zr" (0.6 mmol), THF (7 mL), rt; (2) **3a**, **3c**, or **3e** (0.75 mmol), CuCl (0.05 mmol), THF, reflux. [b] Isolated yields. [c] Acetylene derivative (S_N2 product) was not detected by 300 MHz ^1H NMR.

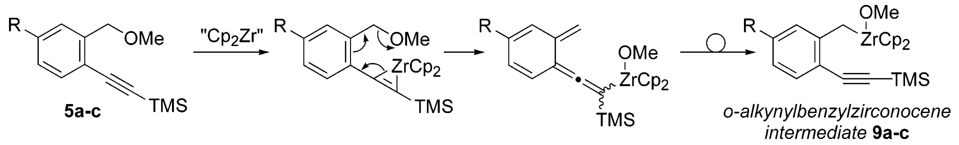
argyl bromide (**3e**) has proceeded with a complete S_N2' process to give the allene product.

Allylations of *o*-alkynylbenzylmethyl ether derivatives **5a**−**c** under the same conditions as for the styrene derivatives **1a**−**c** were also examined, and the results are shown in Table 2. Although a slightly increased quantity of "Cp_2Zr" was required for the complete consumption of the starting material (by TLC), the allylation of **5a** with allyl bromide (**3a**) proceeded to give an allylation product **7a** in a good yield (entry 1). *p*-Methoxy- and *p*-fluorophenyl derivatives **5b** and **5c**, respectively, also reacted with **3a** to give corresponding allylation products **7b**, **7c**, and **7d** in good yields (entries 2−4). Although the clear spectral data of the intermediates generated from **5a**−**c** could not be obtained, we assumed the presence of benzylzirconocene intermediates **9a**−**c** containing an *o*-TMS-alkyne unit as well (Scheme 3).

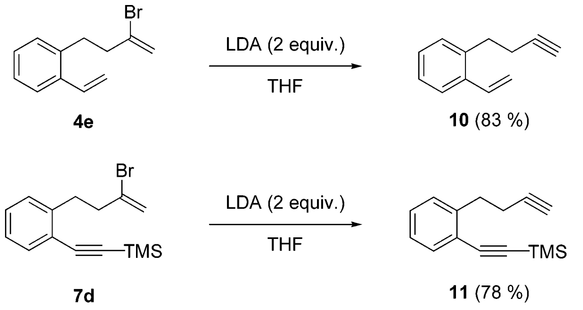
Same as the reactions of the styrene derivative, the reaction of **5a** with propargyl bromide (**3e**) gave an allene derivative **7e** as the sole product in 68% yield (entry 5). In contrast to the allylations of **1a**−**c** and **5a**−**c**, the reaction of *o*-alkoxymethylphenylallene derivative **6** gave a complex mixture, and the desired allylated phenylallene derivative **8** could not be obtained (entry 6).

Although the reactions of propargyl bromide gave allene compounds (**4g**, **7e**), an easy conversion of the allylation product **4e** or **7d** to ene-yne **10** (83% yield) or diyne **11** (78% yield) was achieved by the treatment of **4e** or **7d** with LDA (2 equiv) in THF (Scheme 4).[9] Thus,

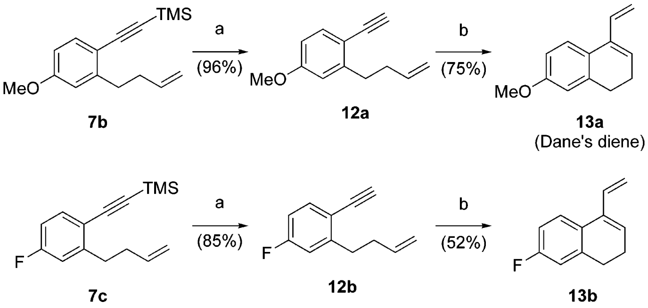
SCHEME 3. Generation of Benzylzirconocene Intermediate 9



SCHEME 4. Transformations of Vinyl Bromide Derivatives to Acetylene Derivatives



SCHEME 5. Enyne Metathesis[a]



[a] Reagents and conditions: (a) TBAF, THF, rt; (b) second-generation Grubbs catalyst, CH_2Cl_2, rt.

it is possible to introduce a propargyl or allenyl group to the benzylic position by the choice of the reaction.

Recent advances of the ring-closing metathesis (RCM) provide a powerful tool for the synthesis of cyclic compounds with a wide range of ring sizes. The present CuCl-catalyzed allylation of **5b** provides ene-yne compound **7b**. As a synthetic application of the present allylation product **7b**, RCM of ene-yne derivative **7b**, which is expected to give a conjugated diene compound known as Dane's diene **13a**,[10] an important intermediate for the synthesis of estrone,[11] was examined. The preparation of the intermediate **13a** was efficiently carried out by an intramolecular enyne metathesis[12] using Grubbs catalyst[13] (Scheme 4).

Although the direct enyne metathesis of **7b** or **7c** did not proceed even under reflux conditions, intramolecular enyne metathesis (second-generation Grubbs catalyst (5 mol %), CH_2Cl_2, rt) of desilylated acetylene derivatives **12a** proceeded to give Dane's diene **13a** in 75% yield. In enyne metathesis chemistry, a fluorine substituent on the aromatic ring afforded fluorine analogue **13b** in 52% yield (Scheme 4).

In conclusion, we have demonstrated the efficient generation and carbon–carbon bond formation of *o*-alkenyl- or alkynylbenzylzirconocene intermediates with allylic halide derivatives under CuCl-catalyzed conditions. The enyne metathesis of the allylation product derived from the *o*-alknylbenzylzirconocene intermediates with Grubbs catalyst afforded Dane's diene with high efficiency, which is a key intermediate for the estrone synthesis.

Experimental Section

Typical Procedure for Allylations of *o*-Vinylbenzylzirconocene Intermediate. To a solution of Cp_2ZrCl_2 (153 mg, 0.525 mmol) in THF (5 mL) was added *n*-BuLi (1.6 M solution in *n*-hexane, 0.66 mL, 1.05 mmol) at −78 °C, and the mixture was stirred for 1 h. To this solution was added a solution of **1a** (112 mg, 0.5 mmol) in THF (2 mL), and the mixture was gradually warmed to room temperature and stirred for 3 h. To this reaction mixture was added a solution of allyl bromide (65 μL, 0.75 mmol) in THF (1 mL) and CuCl (5 mg, 0.05 mmol), and then the mixture was refluxed for 5 h. After the mixture was cooled to room temperature, 1 M HCl (aq) was added, and the mixture was extracted with ether. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$, and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by flash chromatography (*n*-hexane), and further purification was carried out by MPLC (*n*-hexane) to give **4a** (70 mg, 88%).

1-(3-Butenyl)-2-vinylbenzene (4a). Colorless oil. IR (liquid film): 2937, 1641, 1484, 991, 911, 772, 753. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.53–7.49 (1H, m), 7.26–7.15 (3H, m), 7.02 (1H, dd, J = 17.3, 10.8 Hz), 5.90 (1H, dddd, J = 17.0, 10.3, 6.7, 6.4 Hz), 5.68 (1H, dd, J = 17.3, 1.5 Hz), 5.33 (1H, dd, J = 10.8, 1.5 Hz), 5.12–4.99 (2H, m), 2.83–2.77 (2H, m), 2.39–2.31 (2H, m). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 139.0, 137.8, 136.2, 134.3, 129.3, 127.5, 126.1, 125.6, 115.3, 114.7, 35.2, 32.9. EI-MS (*m/z*): 158 (M^+). Anal. Calcd for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 91.06; H, 8.79.

Typical Procedure for Synthesis of (3-Butynyl)-Derivatives. To a solution of diisopropylamine (140 μL, 1.0 mmol) in THF (5 mL) was added *n*-BuLi (1.6 M solution in *n*-hexane, 0.63 mL, 1.0 mmol) at 0 °C, and the mixture was stirred for 0.5 h at

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(9) Reaction of vinyl chloride derivative **4d** with sodium amide (4 equiv, THF–HMPA) or LDA (2 equiv, THF) gave a trace or a small amount of the desired ene-yne product **10**.

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the same temperature. To this solution was added a solution of **4e** (119 mg, 0.5 mmol) in THF (2 mL), and the mixture was gradually warmed to room temperature. After being stirred for 3 h at room temperature, the reaction mixture was quenched by 1 M HCl (aq) and extracted with ether. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$, and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by flash chromatography (*n*-hexane), and further purification was carried out by MPLC (*n*-hexane) to give **10** (66 mg, 83%).

1-(3-Butynyl)-2-vinylbenzene (10). Colorless oil. IR (liquid film): 1484, 991, 915, 773, 640. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.56−7.52 (1H, m), 7.29−7.23 (3H, m), 7.02 (1H, dd, $J = 17.3$, 11.1 Hz), 5.71 (1H, dd, $J = 17.3$, 1.5 Hz), 5.38 (1H, dd, $J = 11.1$, 1.5 Hz), 2.99 (2H, t, $J = 7.8$ Hz), 2.49 (2H, dt, $J = 7.8$, 2.6 Hz), 2.05 (1H, t, $J = 2.6$ Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 137.4, 136.3, 134.0, 129.3, 127.6, 126.7, 125.8, 115.9, 83.7, 69.0, 32.5, 20.2. EI-MS (*m/z*): 156 (M^+). Anal. Calcd for $C_{12}H_{12}$: C, 92.26; H, 7.74. Found: C, 92.26; H, 7.84.

Typical Procedure for Desilylation. To a solution of **7b** (129 mg, 0.5 mmol) in THF (5 mL) was added TBAF (about 1.0 M solution in THF, 0.75 mL, 0.75 mmol), and the mixture was stirred for 3 h at room temperature. The mixture was poured into water and extracted with ether. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$, and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by column chromatography (*n*-hexane/ether = 50/1), and further purification was carried out by MPLC (*n*-hexane/ethyl acetate = 20/1) to give **12a** (89 mg, 96%).

2-(3-Butenyl)-1-ethynyl-4-methoxybenzene (12a). Colorless oil. IR (liquid film): 2102, 1607, 1495, 1241, 1161, 1039, 914, 811. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.42 (1H, d, $J = 8.2$ Hz), 6.75−6.68 (2H, m), 5.88 (1H, dddd, $J = 17.0$, 10.3, 6.7, 6.4 Hz), 5.07 (1H, dd, $J = 17.0$, 1.7 Hz), 5.02−4.98 (1H, m), 3.81 (3H, s), 3.19 (1H, s), 2.88 (2H, t, $J = 7.8$ Hz), 2.46−2.37 (2H, m). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 159.6, 146.0, 137.8, 134.0, 114.8, 114.4, 113.6, 111.2, 82.3, 79.3, 55.3, 34.6, 34.3. EI-MS (*m/z*): 186 (M^+). Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58; O, 8.59. Found: C, 83.72; H, 7.39.

Typical Procedure for the Intramolecular Enyne Metathesis. To second-generation Grubbs catalyst (10.6 mg, 12.5 μmol) was added a solution of **12a** (46.6 mg, 250 μmol) in CH_2Cl_2 (2.5 mL), and the mixture was stirred for 16 h at room temperature. After solvent was removed under reduced pressure, the residue was purified by column chromatography (*n*-hexane/ether = 50/1) to give Dane's diene **13a** (35.1 mg, 75%). The structure was confirmed by comparison of spectral data with the authentic sample.[14]

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Supporting Information Available: Experimental procedures and characterization data for products **4a**−**g**, **7a**−**e**, **10**, **11**, **12a**,**b**, and **13a**,**b** and for synthesis of starting materials **1a**−**c**, **5a**−**c**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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