Copper-Catalyzed Intermolecular [4+4] and [4+5] Coupling of Zirconacyclopentadienes with Bis(halomethyl)arenes: A New Pathway to Eight- and Nine-Membered Ring Derivatives

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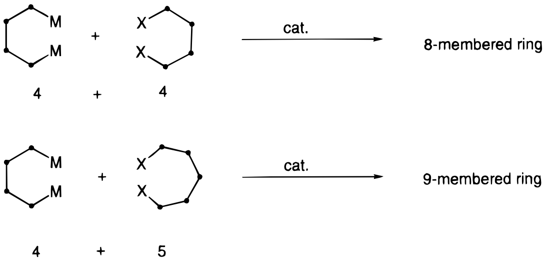
Received June 22, 1998

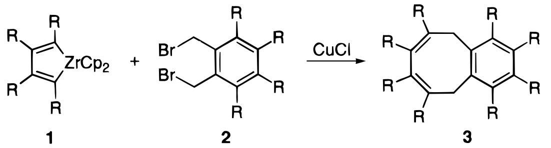
Summary: Zirconacyclopentadienes reacted with 1,2-bis(bromomethyl)benzene and 1,8-bis(bromomethyl)naphthalene in the presence of a catalytic amount of CuCl (10 mol %) to afford highly substituted eight-membered and nine-membered ring compounds in high yields, respectively.

The formation of eight- and nine-membered ring compounds has been attracting considerable attention.[1] However, metal-catalyzed direct intermolecular coupling of two four-carbon units[1,2] or a coupling of a four-carbon unit with a five-carbon unit[1d,3] has been very rare (eq 1), to the best of our knowledge.



(1)

Recently, we have investigated the reactions of zirconacyclopentadienes, which have two Zr-sp^2 carbon bonds, with bis-functionalized substrates, and we have reported the formation of five- to seven-membered ring compounds.[4−6] During the course of our study, we tried the formation of middle-sized compounds such as eight-membered or nine-membered ring derivatives, since the direct intermolecular [4+4] or [4+5] coupling reactions are very rare. In this paper we would like to report a copper-catalyzed intermolecular [4+4] and [4+5] coupling reaction of zirconacyclopentadienes with bis(halomethyl)arenes.



(2)

Typically, zirconacyclopentadiene **1a** (1 mmol), prepared from 3-hexyne and zirconocene according to literature,[7] reacted with 1,2-bis(bromomethyl)benzene **2a** in the presence of a catalytic amount of CuCl (10 mol %) to afford highly substituted benzocyclooctene derivative **3a** in 72% yield at 50 °C in 6 h (eq 2). Use of a stoichiometric amount of CuCl (2 mmol) afforded the same product, **3a**, only in 62% yield. Addition of dimethylpropyleneurea (DMPU, 2.5 mmol) to the reaction mixture increased the yield of **3a** to 93%.[5c] On the other hand, the presence of DMPU showed a retardation effect on the catalytic reaction, resulting in the formation of a complex reaction mixture containing only 30% of **3a**. Some representative examples of the catalytic and stoichiometric reactions are given in Table 1. Reactions of monocyclic zirconacyclopentadienes **1a**,**b** and bicyclic zirconacyclopentadiene **1c** with various bis(bromomethyl)arenes afforded the expected bicyclic or tricyclic derivatives **3a**−**f** in good yields.

Further effort was directed to the extension of this reaction to the formation of compounds with a nine-membered ring using 1,8-bis(bromomethyl)naphthalene **2e** (eq 3). As expected, the CuCl-catalyzed reaction of **1a** with **2e** afforded the nine-membered ring compound

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(1) For reviews see: (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757−5821. (b) Sieburth, S.; Cunard, N. T. *Tetrahedron* **1996**, *52*, 6251−6282. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92. (d) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523−596.

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(4) For five-membered carbocycle formation from zirconacyclopentadienes, for example, see: (a) Takahashi, T.; Sun, W.-H.; Xi, C.; Kotora, M. *Chem. Commun.* **1997**, 2079−2080. (b) Sikora, D. J.; Rausch, M. P. *J. Organomet. Chem.* **1984**, *276*, 21−37.

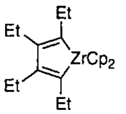
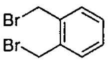
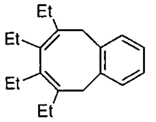
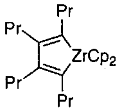
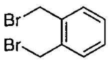
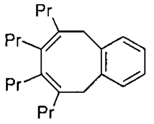
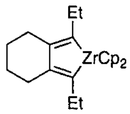
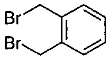
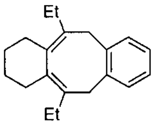
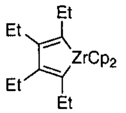
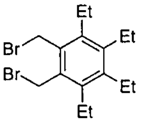
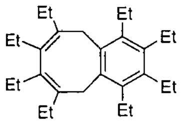
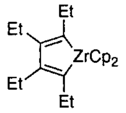
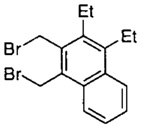
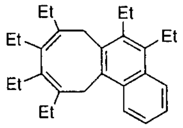
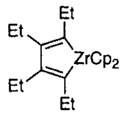
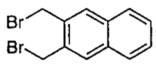
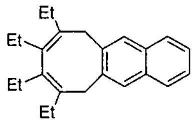
(5) For six-membered carbocycle formation from zirconacyclopentadienes, for example, see: (a) Takahashi, T.; Kotora, M.; Xi, Z. *J. Chem. Soc., Chem. Commun.* **1995**, 361−362. (b) Takahashi, T.; Xi, Z.; Yamazaki, A.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1998**, *120*, 1672−1680. (c) Takahashi, T.; Hara, R.; Nishihara, Y.; Kotora, M. *J. Am. Chem. Soc.* **1996**, *118*, 5154−5155.

(6) For seven-membered carbocycle formation from zirconacyclopentadienes, for example, see: Kotora, M.; Umeda, C.; Ishida, T.; Takahashi, T. *Tetrahedron Lett.* **1997**, *38*, 8355−8358.

(7) (a) Negishi, E.; Swanson, D. R.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1987**, *28*, 917. (b) Negishi, E.; Holms, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.

S0276-7333(98)00530-5 CCC: $15.00
Publication on Web 08/12/1998

Table 1. Reaction of Zirconacyclopentadienes 1 with 1,2-Bis(halomethyl)arenes 2a–d

Zirconacyclopentadiene	Benzyl halide	CuCl (eq)	DMPU (eq)	T/°C	t /h	Product	Yield[a] /%
 **1a**	 **2a**	0.1	-	50	6	 **3a**	72
		2.0	2.5	50	1		93 (67)
 **1b**	 **2a**	0.1	-	50	6	 **3b**	70
		2.0	2.5	50	1		92 (80)
 **1c**	 **2a**	0.1	-	50	3	 **3c**	73
		2.0	2.5	50	1		88 (67)
 **1a**	 **2b**	0.1	-	50	12	 **3d**	67
		2.0	2.5	50	1		95 (50)
 **1a**	 **2c**	0.1	-	50	3	 **3e**	38
		2.0	2.5	50	3		54 (35)
 **1a**	 **2d**	0.1	-	50	3	 **3f**	73
		2.0	2.5	50	1		89 (72)

[a] GC yield. Isolated yields are given in parentheses

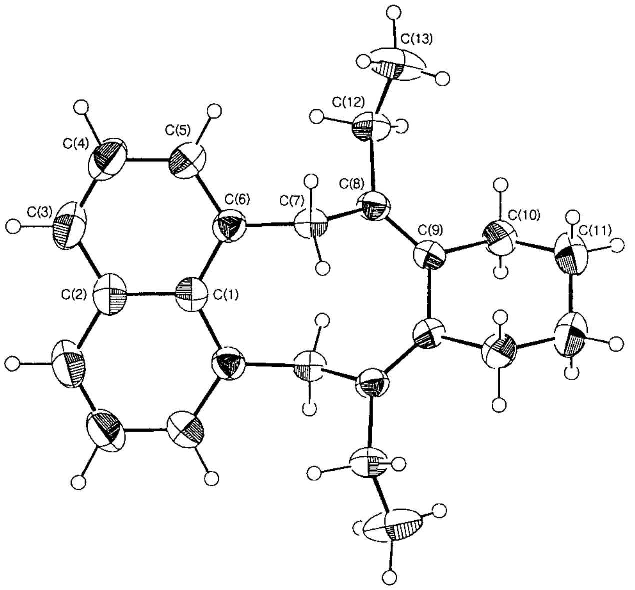
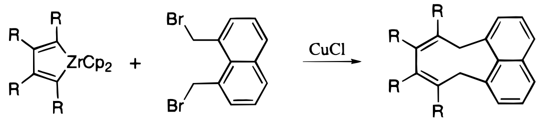


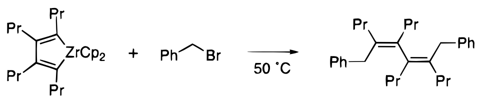
Figure 1. Perspective view of **4c**.

4a in 69% yield. Its stoichiometric reaction with 2.5 equiv of DMPU gave very high yield (92%) of **4a**. The results are summarized in Table 2. The results of the catalytic and stoichiometric reactions are similar to the results obtained with bis(bromomethyl)benzenes. The stoichiometric reaction gave relatively higher yields compared with the catalytic reaction. Single-crystal X-ray analysis of **4c** verified the presence of a nine-membered ring in the compound as shown in Figure 1.



1 **2e** **4** (3)

Reaction of zirconacyclopentadiene **1b** with 2 equiv of benzyl bromide in the presence of a catalytic amount of CuCl (10 mol %) at 50 °C afforded doubly benzylated product **5** in 70% yield. The same effect of DMPU in catalytic and stoichiometric reactions was observed as in the previous cases. Thus, the reaction of **1b** with benzyl bromide in the presence of 2 equiv of CuCl and 2.5 equiv of DMPU afforded **5** in 91% yield. The absence of DMPU led to the formation of a complex reaction mixture.



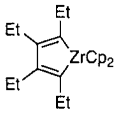
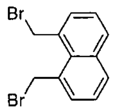
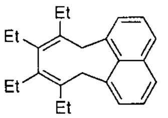
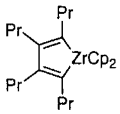
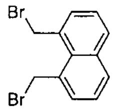
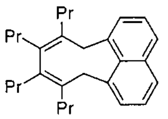
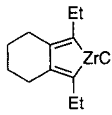
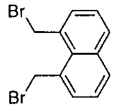
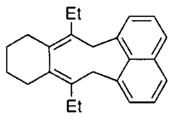
1b **2f** **5** (4)

70% : CuCl (0.1 eq.), 24h
91% : CuCl (2 eq.), DMPU (2.5 eq.), 1h

The successful formation of eight- and nine-membered ring derivatives can be attributed to the structure of the reactants used here. They have structural rigidity due to the presence of conjugated double bonds (a diene moiety) and the aromatic ring moieties (bis(halomethyl)-benzenes). These structural features restrict the number of conformations of both reactants and allow the smooth ring closure to eight- and nine-membered carbocycles.

A plausible catalytic reaction mechanism is shown in Scheme 1. In the first step, zirconacyclopentadiene is

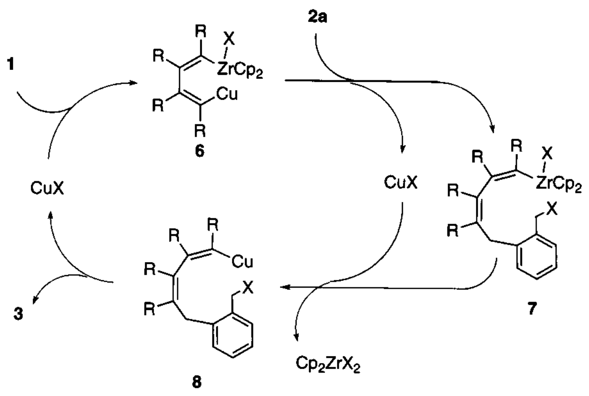
Table 2. Reaction of Zirconacyclopentadienes 1 with 1,8-Bis(bromomethyl)naphthalene 2e

Zirconacyclopentadiene	Benzyl halide	CuCl (eq)	DMPU (eq)	T/°C	t/h	Product	Yield[a] /%
 **1a**	 **2e**	0.1	-	50	3	 **4a**	69
		2.0	2.5	50	1		92 (74)
 **1b**	 **2e**	0.1	-	50	3	 **4b**	67
		2.0	2.5	50	1		91 (72)
 **1c**	 **2e**	0.1	-	50	3	 **4c**	70
		2.0	2.5	50	1		84 (64)

[a] GC yields. Isolated yields are given in parentheses

transmetalated with CuCl[8-12] to mono(cupra)dienylzirconocene intermediate **6**, in which the C–Cu bond reacts intermolecularly with one of the bromomethyl groups forming intermediate **7**. Then the second transmetalation from zirconium to copper occurs to give **8**. The intramolecular coupling of the second C–Cu bond in **8** with the remaining bromomethyl group affords the cyclic compound **3**. However, bisorganocopper species should also be considered as an intermediate in this reaction. It cannot be ruled out.

Scheme 1



Acknowledgment. We thank the Ministry of Education, Science, Sport and Culture, Japan, for support of this study.

Supporting Information Available: All experimental details and crystallographic data, positional and thermal parameters, and lists of bond lengths and angles for **4c** (10 pages). See any current masthead page for ordering and Internet access instructions.

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(8) Transmetalation of a zirconium-sp^2 carbon to copper has been reported; see: Yoshifuji, M.; Loots, M. J.; Schwartz, J. *Tetrahedron Lett.* **1977**, 1303–1306.

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