

Reductive Coupling of Aromatic Dialkyl Acetals Using the Combination of Zinc and Chlorotrimethylsilane in the Presence of Potassium Carbonate

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The treatment of aromatic acetals with zinc and chlorosilane in the presence of potassium carbonate in toluene brought about facile and effective reductive coupling to give the corresponding coupling products.

Vicinal diol and diamine structures are often present in natural products and biologically active molecules, and have been successfully used as chiral ligands in asymmetric synthesis. A number of synthetic methods have been developed for access to the vicinal structures. Among them, the reductive coupling of carbonyl compounds (C=O and C=N) has some advantage in terms of simplicity of the process, and a number of reductants have been developed.¹ However, there are only several reports for sp³ carbon such as acetal, which are a readily available compound and are widely used as a protecting group for carbonyl compounds in organic synthesis,² using either TiCl₄-LiAlH₄,^{3a} [V₂Cl₃(THF)₆]₂[Zn₂Cl₆],^{3b} Al-PbBr₂,^{3c} Ti-TMSCl,^{3d} SmI₂-TFA,^{3e} or TiI₄-Zn.^{3f} We now report a reductive coupling of aromatic dialkyl acetals using the combination of zinc and chlorosilane in the presence of potassium carbonate. The reductive coupling of aromatic dialkyl acetals **1** using these low cost reagents proceeded, giving the corresponding coupling product **2** in good yield.

At first, we demonstrated the reductive coupling of **1a** using reductant, chlorosilane, and additive in toluene. The results are summarized in eq 1 and Table 1. When **1a** was treated with zinc and chlorotrimethylsilane, the coupling product **2a** was obtained in 76% yield (dl/meso = 56/44) along with olefin **3a** formed via pinacol rearrangement of **2a** under acidic conditions (Entry 1).^{4,5} To control the pinacol rearrangement, the influence of base on the reductive coupling was studied. The addition of potassium carbonate and sodium carbonate improved the selectivity and yield of coupling products, giving **2a** as a single product in 98 and 86% yields, respectively (Entries 2 and 3). On the other hand, the addition of potassium bicarbonate, potassium acetate, triethylamine, 1,8-diazabicyclo[5,4,0]-7-undecene, and pyridine impeded the reductive coupling of **1a**, giving unchanged **1a** along with the deprotected benzaldehyde (Entries 4–8). These results suggest that the addition of carbonate ion is useful to control the pinacol rearrangement of **2a** without disturbing the reductive coupling of **1a**.⁶ In this reductive coupling, the amounts of zinc are important: the use of 0.5 or 1.0 mol equiv. amounts of zinc against **1a** resulted in the low yield of **2a** (Entries 9 and 10). We also found that zinc was essential for the reductive coupling of **1a**. Though it is reported that magnesium, aluminum, and manganese, were effective for reductive coupling of benzaldehyde as reductant or co-reductant in the presence of chlorotrimethylsilane,⁷ these reductants cannot work at all (Entries 11–13). Furthermore, the use of copper and sam-

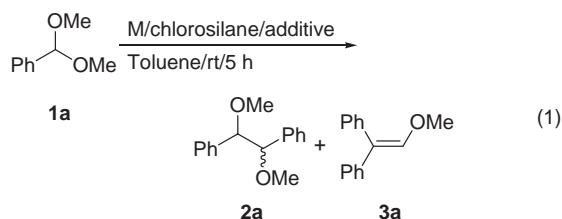


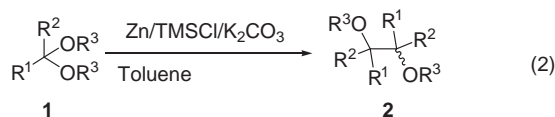
Table 1. Reductive coupling of **1a** in the presence of chlorosilane^a

Entry	Reductant (M)/mmol	Chlorosilane	Additive	Yield /% ^b		dl/meso ^c
				2a	3a	
1	Zn (6.0)	Me ₃ SiCl	none	76	4	56/44
2	Zn (6.0)	Me ₃ SiCl	K ₂ CO ₃	98	0	51/49
3	Zn (6.0)	Me ₃ SiCl	Na ₂ CO ₃	86	0	49/51
4	Zn (6.0)	Me ₃ SiCl	KHCO ₃	0	0	—
5	Zn (6.0)	Me ₃ SiCl	CH ₃ COOK	0	0	—
6	Zn (6.0)	Me ₃ SiCl	Et ₃ N	0	0	—
7	Zn (6.0)	Me ₃ SiCl	DBU	0	0	—
8	Zn (6.0)	Me ₃ SiCl	Pyridine	0	0	—
9	Zn (1.5)	Me ₃ SiCl	K ₂ CO ₃	26	0	50/50
10	Zn (3.0)	Me ₃ SiCl	K ₂ CO ₃	59	0	49/51
11	Mg (6.0)	Me ₃ SiCl	K ₂ CO ₃	0	0	—
12	Al (6.0)	Me ₃ SiCl	K ₂ CO ₃	0	0	—
13	Mn (6.0)	Me ₃ SiCl	K ₂ CO ₃	0	0	—
14	Cu (6.0)	Me ₃ SiCl	K ₂ CO ₃	Trace	0	—
15	Sm (6.0)	Me ₃ SiCl	K ₂ CO ₃	0 ^d	0	—
16	Zn (6.0)	Et ₃ SiCl	K ₂ CO ₃	0	0	—
17	Zn (6.0)	Me ₂ SiCl ₂	K ₂ CO ₃	44	Trace	55/45
18	Zn (6.0)	SiCl ₄	K ₂ CO ₃	53	23	91/9

^aReaction conditions: **1a** (3.0 mmol), reductant, chlorosilane (6.0 mmol), additive (8.0 mmol), rt, 5 h, under N₂. ^bIsolated yield. ^cDetermined by ¹HNMR of crude **2a**. ^dComplex mixture was obtained.

rium did not improve the yield and selectivity (Entries 14 and 15). This reductive coupling of **1a** using zinc in the presence of potassium carbonate was affected by the substituent bearing silyl chloride. The use of chlorotriethylsilane instead of chlorotrimethylsilane did not work the reductive coupling at all (Entry 16). Furthermore, dichloro- and tetrachlorosilane affected the yield and the selectivity: the product **2a** was obtained in moderate yield along with a trace amount of **3a** in the treatment with dichlorodimethylsilane, and the use of tetrachlorosilane showed the diastereoselectivity of **2a** (dl/meso = 91/9), though the product-selectivity was not observed (Entries 17 and 18).⁸

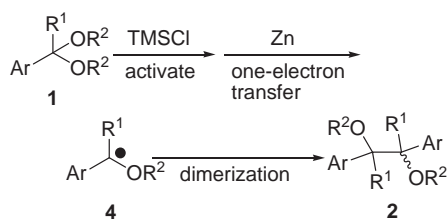
This reductive coupling using zinc and chlorotrimethylsilane in the presence of potassium carbonate was useful for other derivatives **1** and the results are summarized in eq 2 and Table 2.⁹ The reductive coupling of ethyl (**1b**) and isopropyl (**1c**) deriva-

**Table 2.** Reductive coupling of **1** using Zn/TMSCl/K₂CO₃^a

1	R ¹	R ²	R ³	Yield of 2 /%	dl/meso ^c
1b	Ph	H	Et	81	53/47
1c	Ph	H	<i>i</i> -Pr	88	49/51
1d	Ph	H	<i>c</i> -Hexyl	48	50/50
1e	<i>p</i> -MeC ₆ H ₄	H	Me	92	50/50
1f	<i>p</i> -ClC ₆ H ₄	H	Me	79	50/50
1g	<i>o</i> -BrC ₆ H ₄	H	Me	58	46/54
1h	<i>p</i> -CNC ₆ H ₄	H	Me	13 ^d	51/49
1i	<i>p</i> -MeOC ₆ H ₄	H	Me	Complex mixture	—
1j	1-Naphthyl	H	Me	64	49/51
1k	Ph	Me	Me	64	52/48
1l	Ph(CH ₂) ₂	H	Me	0	—
1m	Ph(CH ₂) ₂	Me	Me	Complex mixture	—

^aReaction conditions: **1** (3.0 mmol), zinc (6.0 mmol), chlorotrimethylsilane (6.0 mmol), K₂CO₃ (8.0 mmol), rt, 5–24 h, under N₂. ^bIsolated yield. ^cDetermined by ¹H NMR of crude **2**. ^dTetrachlorosilane was used instead of chlorotrimethylsilane.

tives proceeded smoothly, giving the corresponding coupling products **2b** and **2c** in good yields. In the cyclohexyl group (**1d**), the reductive coupling also took place to give the corresponding coupling product **2d** in moderate yield. It is interesting to note that the substituent alkoxy group on **1** did not much influence the reductive coupling as compared with the substituent on chlorosilane. In the case of *p*-methyl (**1e**), *p*-chloro (**1f**), and *o*-bromo (**1g**) acetals, the reductive coupling products were obtained in moderate to good yields. The derivative having *p*-cyano (**1h**) coupled with great difficulty under the usual reaction conditions; the use of tetrachlorosilane led to the corresponding product **2h** in low yield. In the case of **1i**, only a complex mixture was obtained. In 1-naphthyl acetal **1j** and aromatic ketal **1k**, the similar treatment led to the corresponding coupling products **2j** and **2k**. In the case of aliphatic acetal **1l** and ketal **1m**, however, the reaction did not proceed or gave only a complex mixture.

**Scheme 1.**

It is generally accepted that the reductive coupling of acetals proceeds via a radical process as well as in the case of reductive coupling of carbonyl compounds. Although the detailed pathway is not clear in the present reductive coupling using zinc and chlorotrimethylsilane in the presence of potassium carbonate, the reductive coupling of **1** seems to be triggered by the activation of **1** (Scheme 1). The chlorotrimethylsilane serves as not only a trapping reagent of the eliminated alkoxy group but also a Lewis acid,¹⁰ generating an active species of **1**, which affords the corresponding α -aryl- α -alkoxy-radical **4** by one-electron

transfer from the zinc. Then, the dimerization of **4** leads to the coupling product **2**.

In conclusion, we found that the reductive coupling of aromatic acetals and ketals proceeded using the combination of zinc and chlorosilane in the presence of potassium carbonate, efficiently. Further detailed applications are now in progress.

References and Notes

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- The general procedure for the reductive coupling of **1** and the physical data of **1** and **2** are available as Supporting Information on the CSJ Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.
- The transformation into **3a** from **2a** was observed in the absence of potassium carbonate: when **2a** (100 mg, 413 μ mol, dl/meso = 50/50) was treated with zinc (54.0 mg, 826 μ mol) and chlorotrimethylsilane (105 μ L, 826 μ mol) in 1,2-dichloroethane (5 mL) for 24 h at room temperature, **3a** was obtained in 10% yield (8.4 mg, 40 μ mol) along with unchanged **2a** (60% recovery, 60.0 mg, 248 μ mol, dl/meso = 70/30). In toluene, a trace amount of **3a** was detected by ¹H NMR.
- References are cited in Ref. 1.
- In the treatment of **1a** with zinc and tetrachlorosilane for 1 h instead of 5 h, **2a** (dl/meso = 72/28) was obtained in 18% yield along with **3a** (5% yield).
- Acetals were prepared according to literatures, see: a) D. P. Roelofsen, H. van Bekkum, *Synthesis* **2002**, 419. b) R. Gopinath, S. J. Haque, B. K. Patel, *J. Org. Chem.* **2002**, *67*, 5842.
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