

Reductive Cross-Aldol Reaction Using Bromoaldehyde and an Aldehyde Mediated by Germanium(II): One-Pot, Large-Scale Protocol

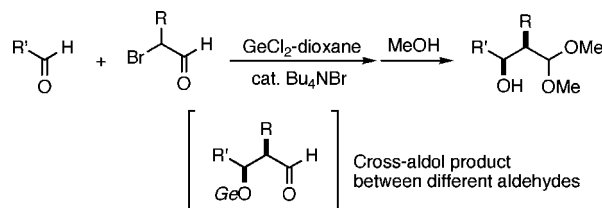
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ABSTRACT



The reaction of α -bromoaldehyde with aldehyde in the presence of GeCl_2 -dioxane gave the *syn*-selective cross-aldol equivalent. A catalytic amount of Bu_4NBr improved the yield and selectivity. The initially formed aldol adduct (β -germoxyaldehyde) did not suffer from over-reaction. This system enabled an intramolecular aldol reaction to give cyclic compounds effectively. One-pot synthetic methodology including bromination of aldehyde followed by cross-aldol reaction with the second aldehyde was successful on a large-scale.

Numerous cross-aldol reactions have been reported for stereoselective carbon–carbon bond formation to give functionalized compounds in organic synthesis.¹ Most of them deal with the reactions of enolates derived from ketones or esters with aldehydes. However, cross-aldol reaction between enolates from aldehydes with aldehydes has rarely been reported probably because the aldol product (β -hydroxyaldehyde) would suffer from undesired further reactions. To avoid this problem, hydroformylation of allylic alcohols can provide an approach to *anti*- β -hydroxyaldehyde derivatives.² A few examples of the stereoselective cross-aldol reactions between aldehydes have recently appeared from some groups and can be classified into two types. One is a direct aldol system that was reported in 1997 as the first stereoselective cross-aldol reaction between aldehydes using a combination

of a base and a Lewis acid to give a *syn*-adduct.³ This system has been developed for asymmetric synthesis by chiral organocatalysis.⁴ These direct reactions may be a simple and ideal methodology, but a self-aldol reaction could be a problem. Therefore, the amount of substrates and the period of their loading should be optimized. The second type is the reaction of aldehyde–enolates with aldehydes. Titanium enolates enabled *anti*-selective reactions.⁵ An excellent system using trichlorosilyl enolates to give either *syn*- or *anti*-products was developed in asymmetric synthesis.⁶

We now report a third type that is a reductive cross-aldol reaction using α -bromoaldehyde, aldehyde, and Ge(II) as a

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reductant.⁷ This system is operationally simple and requires no preparation of metal enolates to give the *syn*-cross-aldol equivalents in high yields.

We examined several low-valent metals as reducing agents for the reaction of 2-bromoheptanal **1a** with benzaldehyde **2a** (Table 1). The typical metal species for reductants such

Table 1. Investigation of Reductants for Reductive Cross-Aldol Reaction

entry	reductant	conditions	yield/%	<i>syn/anti</i>
1	Zn	68 °C, 2 h	0	
2	SmI ₂	−78 °C, 2 h	0	
3	CrCl ₂	rt, 14 h	0	
4	SnCl ₂	rt, 2 h	0	
5	GeCl ₂ –dioxane	rt, 2 h	60	64:36

as Zn, SmI₂, or CrCl₂ gave a complex mixture that probably involves over-reaction products and others (entries 1–3). Gratifyingly, GeCl₂–dioxane⁸ gave the aldol product **3** in 60% yield without any side products (entry 5), while SnCl₂ failed to form **3** with recovery of the starting materials (entry 4).

As isolation of the aldol **3** was difficult because of its instability, and MeOH quenching⁶ was performed to afford the β -hydroxyl dimethyl acetal **4aa** which can be isolated as an aldol equivalent (Table 2, entry 1). On using this workup, reaction conditions were reinvestigated. The results in entries 1–5 suggest that an appropriate coordination is effective. We previously reported a remarkable effect of Bu₄NBr on activation of stannyl enolate.¹⁰ Therefore, Bu₄NBr was added to the reaction mixture and thus strikingly raised the yields of the product **4aa** in the reactions using some solvents. When Et₂O was used with Bu₄NBr (1 mol %), the best yield and selectivity were obtained (entry 7).¹¹ Using SnCl₂ with Bu₄NBr (10 mol %) instead of GeCl₂–dioxane, the reaction proceeded to give a complex mixture without **4aa**, and some amounts of the starting materials (**2a**, 62%, and **1a**, 18%) were recovered.¹² This result indicates that

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(8) We prepare the reductant GeCl₂–dioxane in large-scale by the known method (ref 9). It is noted that the price of prepared GeCl₂–dioxane (price/mol) is not as high as those of SmI₂ or CrCl₂ that are widely used in synthetic chemistry as useful reductants.

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(11) The use of GeBr₂–dioxane and GeI₂ instead of GeCl₂–dioxane under the same conditions as in entry 7 gave lower yields of 72% (80:20) and 27% (88:12), respectively.

Table 2. Optimization of Reaction Conditions^a

entry	solvent	additive	yield/%	<i>syn/anti</i>
1	THF		57	70:30
2 ^b	Et ₂ O		11	57:43
3	DMF		0	
4	hexane		0	
5	CH ₂ Cl ₂		18	47:53
6	THF	Bu ₄ NBr	52	68:32
7	Et ₂ O	Bu ₄ NBr	86	83:17
8	DMF	Bu ₄ NBr	0	
9	hexane	Bu ₄ NBr	56	82:18
10	CH ₂ Cl ₂	Bu ₄ NBr	63	79:21

^a All reactions were performed using bromoaldehyde **1a** (0.6 mmol), benzaldehyde **2a** (0.6 mmol), and GeCl₂–dioxane (0.6 mmol) in solvent (2 mL) at rt for 2 h. ^b 4 h.

further nucleophilic addition to the initially formed aldol adduct (stannoxide) occurs in the reaction course. On the contrary, the GeCl₂ system provided a clean reaction to synthesis of **4aa** without over-reactions. The addition order is also important: The bromoaldehyde should be the last reagent to be added because premixing of the bromoaldehyde and GeCl₂ caused lower yields.

We explored several sets of representative bromoaldehydes **1** and aldehydes **2** (Table 3). In all cases, the *syn*-cross-aldol products **4** were predominantly obtained in moderate to high yields. The aromatic, primary, and secondary aldehydes were applicable to this system. In the reaction of **1a** with **2b**, an increased amount of Bu₄NBr improved the diastereoselectivity (entries 2 and 3). The secondary aldehyde **2c** gave the product **4ac** (entry 4) but the tertiary one (pivalaldehyde) gave no desired product. The β -branched bromoaldehyde **1b** also gave the product **4ba** in high yield (entry 5). The reaction with benzaldehydes bearing either an electron-donating or -withdrawing group took place effectively (entries 7–9). In the reaction with aliphatic aldehydes **2b** and **2c** bearing α -hydrogens, this reductive system certainly gave a reliable result to synthesize only the cross-aldol adducts (entries 2–4, 10–12) without any homoaldol species.

The brominated bis-aldehyde **5** effectively provided the cyclic aldol derivative **6** (Scheme 1). This type of intramolecular reaction (bromoaldehyde + CHO) has not been reported as far as we know. Instead of GeCl₂–dioxane, we tried using SmI₂, which mediates intramolecular Reformatsky reactions (bromoester + CHO),¹³ but obtained only a complicated mixture.

One-pot synthesis including bromination¹⁴ of the first aldehyde **7** followed by the reductive cross-aldol reaction

(12) This procedure was performed without MeOH quenching. The use of SnCl₂ with Bu₄NBr (1 mol %) resulted in almost no reaction.

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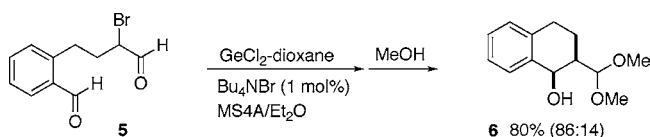
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Table 3. Reductive Cross-Aldol Reaction^a

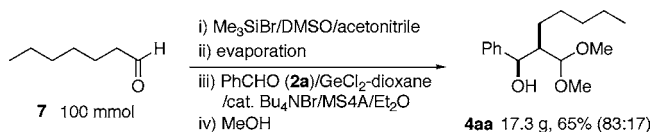
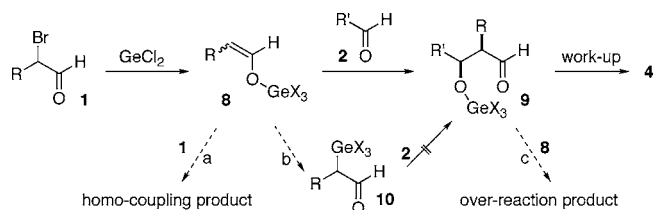
entry	bromoaldehyde	aldehyde	product	yield/% (syn:anti)
1		2a PhCHO		4aa 86 (83:17)
2	1a	2b CH ₃ (CH ₂) ₄ CHO		4ab 78 (79:21) 74 (84:16)
4	1a	2c cyclohexanecarbaldehyde		4ac 70 (80:20)
5 ^{c,d}	1b 2-bromo-3-methylpentanal	2a PhCHO		4ba 85 (84:16)
6	1c 2-bromo-3-phenylpentanal	2a R = H		4ca 75 (87:13)
7 ^{c,d}	1c	2a R = H		4cb 75 (90:10)
8 ^{c,d}	1c	2d R = Me		4cd 70 (88:12)
9 ^{c,d,e}	1c	2e R = NO ₂		4ce 68 (91:9)
10	1c	2b CH ₃ (CH ₂) ₄ CHO		4cb 68 (84:16)
11 ^c	1c	2c cyclohexanecarbaldehyde		4cc 53 (85:15)
12 ^{c,f}	1c	2c		4cc 64 (84:16)

^a All reactions were performed using bromoaldehyde **1** (0.6 mmol), benzaldehyde **2** (0.6 mmol), GeCl₂-dioxane (0.6 mmol), and Bu₄NBr (1 mol %) in Et₂O (2 mL) at rt for 2 h and quenched by methanol. ^b Bu₄NBr (5 mol %). ^c Bu₄NBr (0.5 mol %). ^d 0 °C, 4 h. ^e EtOAc was used as a solvent. ^f Slow addition of bromoaldehyde for 5 min.

with another aldehyde **2a** succeeded to give **4aa** (Scheme 2). It is also interesting that our procedure can be performed on a large-scale. In fact, 100 mmol scale synthesis gave **4aa** in 65% yield (17.3 g) in pure form after column chromatography.

Scheme 1. Intramolecular Cross-Aldol Reaction

A plausible reaction course is shown in Scheme 3. GeCl₂-dioxane gives the germynyl enolate **8** which adds to aldehyde **2** to afford the cross-aldol germoxide **9**. The loaded Bu₄NBr acts as a ligand to the germanium center and increases the nucleophilicity of the enolate **8**. The carbonyl addition

Scheme 2. One-Pot and Large-Scale Synthesis**Scheme 3.** Plausible Reaction Course and Undesired Side Paths (Dashed Arrow)

proceeds through an acyclic transition state to give *syn*-product predominantly. This reaction could suffer from undesired side reactions as shown by dashed arrows in Scheme 3: (a) formation of homo-coupling product of **1** through **8**, (b) tautomerization of **8** into α -germylaldehyde **10** which is less nucleophilic than **8**,¹⁵ (c) further transformation of the adduct **9** into an over-reaction product. In fact, the mixture of **1a** and GeCl₂-dioxane with Bu₄NBr (1 mol %) in the absence of aldehyde **2** gave a complicated mixture probably because of paths a and b. However, fast generation of **8** and its carbonyl addition to **2** predominate over these side paths. The most important point is that the formed germoxide **9** does not suffer from further nucleophilic additions (path c), while the SnCl₂ system resulted in over-reaction. The germanium(IV) in **9** seems to have much lower Lewis acidity than the stannyl analogues.

To get preliminary information for Lewis acidity of Ge(IV), the acidity of GeCl₄ is estimated as compared with other typical Lewis acids (TiCl₄ and SnCl₄) by measurement of $\delta(^{13}\text{C})$ or ν/cm^{-1} of the carbonyl group in heptanal (Table 4).¹⁶ As expected, significant downfield shift in ¹³C NMR

Table 4. Effect of Metal Halides on $\delta(^{13}\text{C})$ ^a or ν/cm^{-1} ^b of Carbonyl Group in Heptanal

entry	metal halide	$\delta(^{13}\text{C})/\text{ppm}$	$\Delta\delta(^{13}\text{C})/\text{ppm}$	ν/cm^{-1}	$\Delta\nu/\text{cm}^{-1}$
1	none	202.61	0	1728	0
2	TiCl ₄	219.13	+16.52	1674	-46
3	SnCl ₄	216.89	+14.28	1668	-40
4	GeCl ₄	201.70	-0.91	1728	0

^a NMR: heptanal and metal halide (2.4 equiv) in CDCl₃. ^b IR: heptanal and metal halide (1.0 equiv) in CCl₄.

and a marked decrease in the carbonyl stretching frequency in the IR spectrum for the carbonyl group were observed with TiCl₄, which is a typical Lewis acid. SnCl₄ also showed a similar change with TiCl₄. Surprisingly, neither the chemical shift nor carbonyl stretching was affected by GeCl₄. This result shows the low Lewis acidity of GeCl₄ as compared with SnCl₄. It also indicates the germanium center

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does not activate the carbonyl group in **9** but might even retard further addition owing to its steric factor.¹⁷

In conclusion, a novel type of the cross-aldol reaction between different aldehydes effectively proceeded in the reaction of α -bromoaldehyde with aldehyde mediated by GeCl_2 -dioxane. A catalytic amount of Bu_4NBr improved the yield and selectivity. The germanium species is reputed to be of low toxicity,⁹ easy to handle for conventional operation under nitrogen, and not more expensive than some typical reductants used in organic synthesis. The appropriate reducing ability of germanium(II) and the low Lewis acidity

(17) In NMR study of the Bu_4NBr -catalyzed reaction between **1a** and **2a** mediated by GeCl_2 -dioxane in CD_2Cl_2 , the adduct **9** and free dioxane were observed. Therefore, the dioxane has no important role for decreasing of Lewis acidity of germanium(IV) in **9**.

of germanium(IV) accomplished a clean reaction pathway without side reactions.

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Supporting Information Available: Experimental procedures, spectroscopic details of new compounds, and data of single-crystal X-ray analysis of **6** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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