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Germanium(II)-Mediated Reductive Cross-Aldol Reaction of Bromoaldehydes with Aldehydes: NMR Studies and ab Initio Calculations

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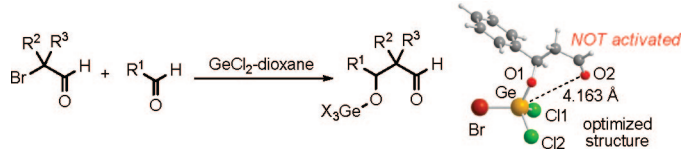


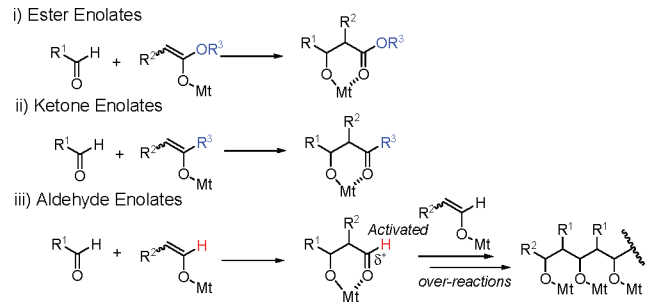
A highly practical reductive cross-aldol reaction of α-bromoaldehydes with various aldehydes has been developed using $Ge(II)Cl_2$ to produce aldehyde germanium(IV) aldolates, which were directly transformed to various multifunctionalized compounds. A remarkable change in stereoselectivity depended on the α-bromoaldehydes employed; secondary α-bromoaldehydes gave syn selectivities, while tertiary α-bromoaldehydes accomplished the synthesis of anti-selective aldol products with a quaternary carbon center. NMR studies and X-ray analysis strongly suggested the formation of germanium enolate in the reaction of α-bromoaldehyde **2h** with $GeCl_2$−dioxane. Detailed mechanistic studies, including NMR analysis and ab initio calculations, revealed the generation of stable germanium aldolates, which was due to the remarkably low Lewis acidity of the germanium(IV).

Introduction

A stereoselective aldol reaction is one of the most fundamental and powerful methods in organic synthesis. Owing to their broad significance, considerable efforts have been devoted to the development of the methodology.[1] However, most of them deal with the reactions of metal enolates derived from ketones or esters with aldehydes (Scheme 1, eq i and ii). The reaction using aldehyde-enolates (Scheme 1, eq iii) is still a challenge, because the formyl group in the produced aldolates (*β*-metaloxyaldehydes) suffers from several undesired over-reactions (e.g., further reaction with enolates, dehydration, and oligomerization).[2]

There are a few examples of the stereoselective cross-aldol reaction using a metal enolate prepared from an aldehyde. An anti-selective cross-aldol reaction has been achieved by titanate-type aldehyde enolates.[3] The first diastereo- and enantioselective cross-aldol reaction between aldehydes was achieved using trichlorosilyl enolates with a chiral Lewis base catalyst.[4,5] More

SCHEME 1. Cross-Aldol Reaction of Metal Enolates with Aldehydes



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(1) (a) Selected reviews: *Comprehensive Organic Syntheses*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 2, pp 99−319. (b) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095–1120. (c) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; Vols. 1, 2.

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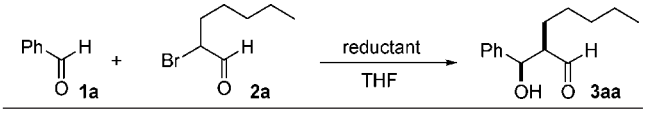
TABLE 1. Effect of Reductants on the Reductive Cross-Aldol Reaction[a]



entry	reductant	conditions	yield (%)[b]
1	$GeCl_2$−dioxane (1 equiv)	rt, 2 h	60
2	Zn (1 equiv)	68 °C, 2 h	0
3	SmI_2 (2 equiv)	−78 °C, 2 h	0
4	$CrCl_2$ (3 equiv)	rt, 14 h	0
5	InCl (1 equiv)	rt, 3 h	0
6	In (1 equiv)	68 °C, 2 h	0
7[c]	$SnCl_2$ (1 equiv)	rt, 2 h	0

[a] Reaction conditions: **1a** (0.6 mmol), reductant, **2a** (0.6 mmol), and THF (2 mL). [b] Yield determined from ^{1}H NMR spectrum. [c] Recovery, **2a** (65%).

recently, the aldehyde enolates with a bulky silyl group were found to be effective for the aldol addition of aldehyde enolates.[6] Aldehyde-derived encarbamates (as an alternative to metal enolate) achieved diastereo- and enantioselective addition to aldehydes.[7] In contrast to systems that employ a prepared nucleophile such as metal enolate, the direct aldol reaction between aldehydes have received increasing attention.[8] The direct systems may be ideal in terms of atom efficiency, but a homoaldol reaction can become a problem. We recently disclosed a reductive cross-aldol reaction using α-bromoaldehydes and aldehydes, in which germanium(II) was employed as a reductant.[9,10] This system was operationally simple and required no isolation of reactive metal enolates.[11] Herein, we report a detailed and systematic investigation of the Ge(II)-mediated system, including improvement of the reaction conditions, NMR experiments, X-ray analysis, and ab initio calculations to clarify a key feature of the system. We also demonstrate successive transformations of the produced germanium aldolates to give a variety of functionalized compounds in a one-pot treatment.

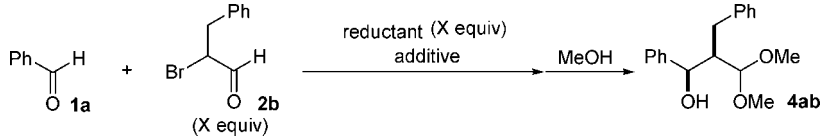
Results and Discussion

1. Reductive Cross-Aldol Reaction of Secondary α-Bromoaldehydes with Aldehydes. Our investigations started with a search of low-valent metals for the reductive cross-aldol reaction between benzaldehyde **1a** and 2-bromoheptanal **2a** (Table 1). Among the metals examined, only $GeCl_2$−dioxane effectively afforded the cross-aldol product **3aa** (entry 1). In contrast, Zn, SmI_2, $CrCl_2$, InCl, and In, generally known as favorable reductants, gave a complex mixture that probably involved over-reacted products (entries 2−6). The use of $SnCl_2$ resulted in a recovery of the starting bromoaldehyde **2a** (65%), which indicates insufficient reduction ability of $SnCl_2$ (entry 7).

Next, we optimized the reaction conditions for the addition of benzaldehyde **1a** and bromoaldehyde **2b**. (Table 2). As the generated aldol (β-hydroxyaldehyde) was unstable for isolation, MeOH-quenching was performed to afford the β-hydroxyl dimethyl acetal **4ab** as an aldol equivalent. The reaction in THF gave the product **4ab** in moderate yield (entry 1), while only the debromination of **2b** was observed in DMF to give a considerable amount (59%) of 3-phenylpropanal (entry 2). Less basic solvents, Et_2O and dioxane, hardly afforded the product, and bromoaldehyde **2b** was recovered (entries 3 and 4). The addition of a catalytic amount of Bu_4NBr, which was previously reported, drastically improved the yield in dioxane solvent (entry 5). The use of PPh_3 was found to give higher diastereoselectivity than Bu_4NBr (entry 6). These results indicate that it is very important to use solvents or additives with appropriate coordination ability. The use of 1.3 equiv of bromoaldehyde **2b** and $GeCl_2$−dioxane effectively raised the yield (entry 7). Moreover, employing 1.5 equiv of **2b** and $GeCl_2$−dioxane and the slow addition of **2b** at 0 °C increased the product yield to 92% (entry 8). Although the use of $SnCl_2$ with Bu_4NBr (10 mol %) promoted the consumption of bromoaldehyde **2b**, in contrast to the results obtained when the reaction was carried out without Bu_4NBr (Table 1 entry 7), only a complicated mixture was obtained (entry 9).

Under optimized conditions, we explored the scope of secondary α-bromoaldehydes and aldehydes (Table 3). High yields were obtained in the reactions with both aromatic aldehydes bearing electron-withdrawing groups and those bearing donating groups (entries 2−7). Aliphatic aldehyde **1f**, however, gave only a modest yield under the optimized conditions (condition A: 1 mol % of PPh_3, 0 °C) (entry 8). In this case, the use of 5 mol % of PPh_3 at room temperature (condition B) increased the yield to 75% (entry 9). This procedure achieved highly reliable results in the reaction with aliphatic aldehydes bearing an α-hydrogen, with the exception

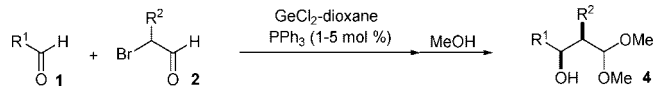
TABLE 2. Reductive Cross-Aldol of Bromoaldehyde 2b with Aldehyde 1a[a]



entry	reductant	*X* (equiv)	additive	solvent	conditions	yield (%)[b]	syn:anti
1	$GeCl_2$−dioxane	1.0	none	THF	rt, 2 h	36	82:18
2[c]	$GeCl_2$−dioxane	1.0	none	DMF	rt, 2 h	0	
3[d]	$GeCl_2$−dioxane	1.0	none	Et_2O	rt, 2 h	9	80:20
4[e]	$GeCl_2$−dioxane	1.0	none	dioxane	rt, 2 h	2	
5	$GeCl_2$−dioxane	1.0	Bu_4NBr (5 mol %)	dioxane	rt, 1 h	71	87:13
6	$GeCl_2$−dioxane	1.0	PPh_3 (5 mol %)	dioxane	rt, 1 h	71	91:9
7	$GeCl_2$−dioxane	1.3	PPh_3 (5 mol %)	dioxane	rt, 1 h	89	89:11
8[f]	$GeCl_2$−dioxane	1.5	PPh_3 (1 mol %)	Et_2O	0 °C, 4 h	92	91:9
9[g]	$SnCl_2$	1.0	Bu_4NBr (10 mol %)	Et_2O	rt, 2 h	0	

[a] Reaction conditions: **1a** (0.6 mmol), $GeCl_2$−dioxane (*X* equiv), **2b** (*X* equiv), additive, and solvent (2 mL). [b] Yield determined from ^{1}H NMR spectrum. [c] Recovery, 3-phenylpropanal (59%). [d] Recovery, 3-phenylpropanal (35%) and **2b** (23%). [e] Recovery, 3-phenylpropanal (44%) and **2b** (10%). [f] **2b** was slowly added for 30 min. [g] Recovery, **2b** (7%).

TABLE 3. Reaction of Various Aldehydes and Secondary Bromoaldehydes[a]

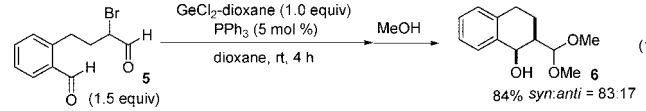


entry	conditions	aldehyde	bromoaldehyde	product	yield (%)[b]	*syn:anti*
1	A	**1a** R=H		**4ab**	92 (82)	91:9
2	A	**1b** =Me		**4bb**	91	89:11
3	A	**1c** =Br	**2b**	**4cb**	89 (61)	92:8
4	A	**1d** =COOMe		**4db**	86 (76)	91:9
5[c]	A	**1e** =NO_2		**4eb**	91	96:4
6	A	**1a**	**2a**	**4aa**	91	86:14
7	B	**1a**	**2c**	**4ac**	78	89:11
8	A	**1f**	**2b**	**4fb**	57	93:7
9[d]	B	**1f**	**2b**	**4fb**	75	91:9
10	B	**1f**	**2a**	**4fa**	76	87:13
11	B	**1g**	**2b**	**4gb**	66 (51)	91:9
12	B	**1h**	**2b**	**4hb**	17	88:12
13	C	**1h**	**2b**	**4hb**	66 (61)	88:12
14[e]	B	**1i**	**2b**	**4ib**	63	87:13
15[e]	B	**1i**	**2a**	**4ia**	61	82:18
16	B	**1j**	**2a**	**4ja**	59 (62)	91:9
17	B	**1k**	**2a**	**4ka**	67 (60)	89:11

[a] Condition A: Slow addition of **2** (0.9 mmol) in Et_2O for 30 min to the mixture of **1** (0.6 mmol), $GeCl_2$−dioxane (0.9 mmol), PPh_3 (0.006 mmol), and Et_2O, 0 °C, 4 h. Condition B: **1** (0.6 mmol), $GeCl_2$−dioxane (0.72 mmol), **2** (0.72 mmol), PPh_3 (0.03 mmol), and dioxane, rt, 1 h. Condition C: Slow addition of $GeCl_2$−dioxane (0.78 mmol, DME solution) for 30 min to the mixture of **1h** (0.6 mmol), **2b** (0.78 mmol), PPh_3 (0.03 mmol), and DME, rt, 1 h. [b] Yield determined from ^1H NMR spectrum. Values in parentheses indicate isolated yield in different batch reactions in different scale (see Supporting Information). [c] Solvent: DME. [d] Slow addition of **2** for 15min. [e] PPh_3 (1 mol %) was used.

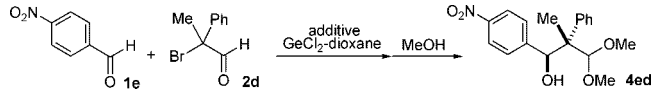
of 4-pentenal (**1h**) (entries 8−15). The low yield from **1h** was improved by the slow addition of $GeCl_2$−dioxane in DME (condition C) (entry 13). Notably, secondary aldehyde **1i** also provided the corresponding cross-aldol products (entries 14 and 15).[12] In the reactions of α-bromoaldehyde **2a** with aldehydes **1j** and **1k**, which have a C_{sp2}-halide moiety, $GeCl_2$−dioxane selectively reacted with **2a** to give the desired aldol products (entries 16 and 17).

The bis-aldehyde **5** provided the cyclic aldol derivative **6** in high yield (eq 1). As far as we know, this type of intramolecular reductive aldol reaction (bromoaldehyde + CHO) has not been previously reported. The use of SmI_2, a well-known promoter of an intramolecular Reformatsky reaction,[13] instead of $GeCl_2$−dioxane gave only a complicated mixture.



The highly practical, one-pot, large-scale synthesis (100 mmol) of cross-aldol product **4aa** was demonstrated (eq 2). Bromination[14] of the aldehyde **1l** was followed by a reductive cross-aldol reaction with another aldehyde **1a**, providing the

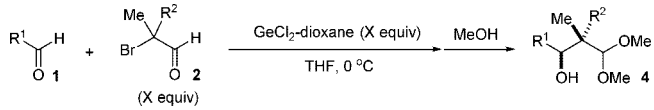
TABLE 4. Reductive Cross-Aldol of Tertiary Bromoaldehyde 2d with Aldehyde 1e[a]



entry	solvent	additive	conditions	anti:syn	yield (%)[b]
1	dioxane	none	rt, 2 h	80:20	44
2	dioxane	PPh_3 (5 mol %)	rt, 2 h	83:17	83
3	THF	none	rt, 2 h	88:12	73
4	THF	none	0 °C, 2 h	92:8	67
5	THF	none	0 °C, 6 h	94:6	83
6[c]	THF	none	0 °C, 6 h	95:5	89

[a] Reaction conditions: **1e** (0.6 mmol), additive, **2d** (0.6 mmol), $GeCl_2$−dioxane (0.6 mmol), and solvent (2 mL). [b] Yield determined from ^1H NMR spectrum. [c] Run using 0.72 mmol of **2d** and $GeCl_2$−dioxane.

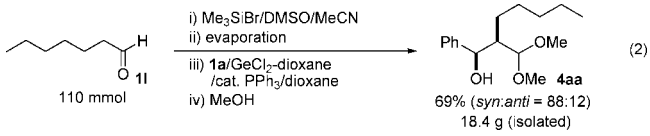
TABLE 5. Diastereoselective Construction of Quaternary Carbon Center[a]



entry	time	X (equiv)	**1**	R^1	**2**	R^2	product	yield (%)[b]	syn:anti
1	6	1.2	**1e**	4-NO_2−C_6H_4	**2d**	Ph	**4ed**	89	5:95
2	6	1.2	**1e**	4-NO_2−C_6H_4	**2d**	Ph	**4ed**	80[c]	6:94
3	12	1.2	**1m**	4-CN−C_6H_4	**2d**	Ph	**4md**	83(73)	8:92
4	12	1.2	**1n**	4-CF_3−C_6H_4	**2d**	Ph	**4nd**	77(71)	8:92
5	4	1.0	**1o**	$PhCH_2CH_2$	**2d**	Ph	**4od**	73	7:93
6	12	1.0	**1p**	$(CH_3)_2CHCH_2$	**2d**	Ph	**4pd**	66	8:92
7	12	1.0	**1g**	$BnOCH_2CH_2$	**2d**	Ph	**4gd**	64	9:91
8[d]	4	2.0	**1h**	CH_2=$CHCH_2CH_2$	**2d**	Ph	**4hd**	85(56)	9:91
9	9	1.2	**1e**	4-NO_2−C_6H_4	**2e**	2-Naph	**4ee**	84(80)	5:95
10	10	1.0	**1o**	$PhCH_2CH_2$	**2e**	2-Naph	**4oe**	70(77)	10:90
11[e,f]	2	1.2	**1e**	4-NO_2−C_6H_4	**2f**	*t*-$BuC_6H_4CH_2$	**4ef**	91	28:72
12[e,g]	4	1.0	**1a**	Ph	**2g**	Me	**4ag**	83	-
13[e,h]	2	1.0	**1o**	$PhCH_2CH_2$	**2g**	Me	**4og**	93	-

[a] Reaction conditions: **1** (0.6 mmol), **2** (X equiv), $GeCl_2$−dioxane (X equiv), and THF (2 mL). [b] Yield determined from ^1H NMR spectrum. Value in parentheses indicates isolated yield in different batch reactions in different scale (see Supporting Information). [c] Isolated yield on 10 mmol scale. [d] Addition of **1h** to the premixed solution of **2d** and $GeCl_2$−dioxane. [e] Reaction temperature: rt. [f] Obtained as a *β*-hydroxyaldehyde. [g] Reaction conditions: **1** (0.6 mmol), **2** (0.6 mmol), $GeCl_2$−dioxane (0.6 mmol), PPh_3 (0.03 mmol), and dioxane (2 mL). [h] Reaction conditions: **1** (0.6 mmol), **2** (0.6 mmol), $GeCl_2$−dioxane (0.6 mmol), PPh_3 (0.06 mmol), and dioxane (2 mL).

pure adduct **4aa** in 69% isolated yield (18.4 g) after column chromatography.



2. Reductive Cross-Aldol Reaction of Tertiary α-Bromoaldehydes with Aldehydes. To broaden the scope of this methodology, tertiary α-bromoaldehydes were treated. The diastereocontrolled construction of a quaternary carbon center by cross-aldol reaction was limited.[15]

Initially, we tested the reaction of tertiary bromoaldehyde **2d** with *p*-nitrobenzaldehyde **1e** (Table 4). Surprisingly, *anti*-aldol **4ed** was predominantly obtained, whereas secondary bromoaldehydes gave syn-selective adducts (Table 3). The addition of a catalytic amount of PPh_3 improved the yield from 44% to 83% (entries 1 and 2). The use of THF solvent avoided the addition of PPh_3 and gave both a good yield and selectivity (entry 3). Higher yield and diastereoselectivity were obtained by lowering the temperature with a longer reaction time (entries 4 and 5). Finally, the use of a slight excess amount of bromoaldehyde **2d** and $GeCl_2$−dioxane provided a satisfactory result (entry 6, 89% yield, 95:5 selectivity).

Table 5 shows the results of the stereoselective construction of quaternary carbon center using tertiary α-bromoaldehydes. Electron deficient aromatic aldehydes and primary aliphatic aldehydes both provided the aldol products in high anti selectivities (entries 1−10).[16] In the reaction with bromoaldehyde **2f**, a smaller steric difference between the two substituents at α position (*t*-$BuC_6H_4CH_2$ vs Me) lowered the selectivity (entry 11). α,α-Dimethyl bromoaldehyde **2g** furnished products with no stereogenic quaternary center in high yields (entries 12 and 13).

3. Observation of Reactive Species. To gain insight into the active species, an NMR measurement was performed on the mixture of bromoaldehyde **2a** and $GeCl_2$−dioxane in THF-d_8 without aldehyde. Unfortunately, decomposition of **2a** into complicated mixture presumably because of homocoupling and/or over reactions was observed. Therefore, we prepared **2h** whose enol form could be stabilized and observed for NMR study illustrated in eq 3.[17]

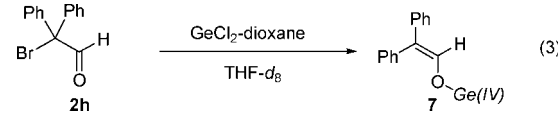


Figure 1 shows the ^1H and ^{13}C NMR spectra of germanium enolate **7**. Significantly, in the ^1H NMR spectrum no peak

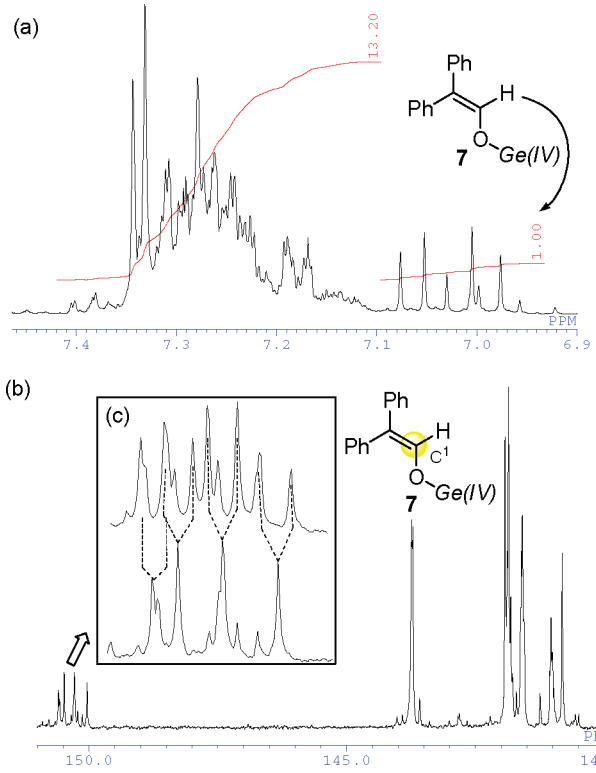
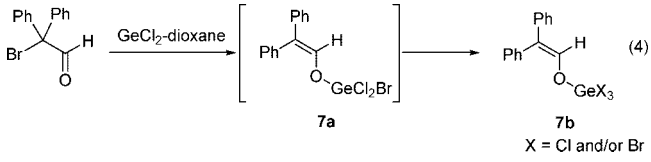
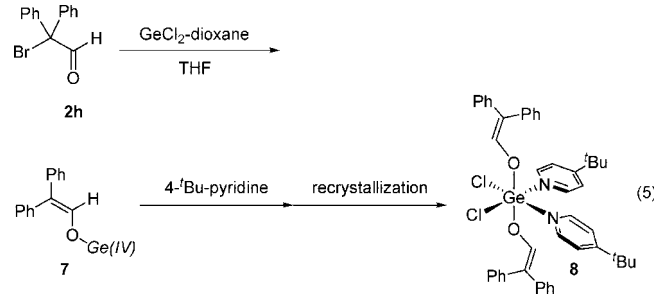


FIGURE 1. (a) ^{1}H NMR and (b) $^{13}C\{^{1}H\}$ NMR spectra of germanium enolate **7**. (c) $^{13}C\{^{1}H\}$ NMR and ^{13}C off-resonance decoupled spectra of **7**.

corresponding to a formyl group around 9−10 ppm was observed, and several singlet signals appeared around 7 ppm, which would correspond to vinyl protons (H^1) of germanium enolate **7** (Figure 1a). Similarly, the ^{13}C NMR spectrum showed several signals around 150 ppm (Figure 1b). The off-resonance decoupled spectra of the signals around 150 ppm exhibited doublet multiplicities (Figure 1c), and therefore, the signals corresponded to vinyl carbon (C^1). These results suggest the formation of several kinds of germanium enolates. We envision a halogen exchange taking place on initially generated germanium enolate **7a** to form different kinds of germanium enolates **7b** (eq 4).

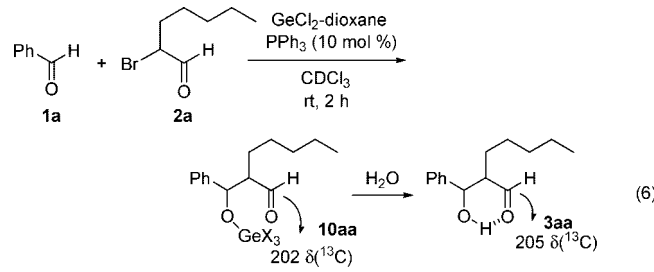


Next, germanium enolate **7** was treated with various ligands in order to stabilize it. When **7** was treated with 4-*t*-butylpyridine, the resulting pale yellow precipitates were soluble in several organic solvents, such as THF, CH_2Cl_2, and $CHCl_3$. The NMR spectra (in $CDCl_3$) indicated the formation of the pyridine adduct of germanium enolates (see Supporting Information). X-ray analysis of the single crystals obtained by recrystallization from THF/hexane indicated the formation of a hexa-coordinate germanium enolate bearing two vinyloxy moieties **8** (eq 5). An ORTEP view of **8** is shown in the Supporting Information. Although we cannot discuss the structural details, because of unsatisfactory refinement, this provides strong evidence of the formation of germanium enolate from α-bromoaldehyde.



4. Mechanistic Insight. A possible reaction path is depicted in Scheme 2. $GeCl_2$−dioxane reacts with α-bromoaldehyde **2** to generate germanium(IV) enolate **9**. Basic species such as THF or PPh_3 coordinate the germanium enolate to increase the nucleophilicity.[18] Enolate **9** then reacts with aldehyde **1** to give germanium aldolate **10**, which is obtained as dimethylacetal **4** after MeOH workup. One of the most difficult features of the cross-aldol reaction using the aldehyde enolate is that the produced metal aldolate **10**suffers from undesired over-reactions. The use of $SnCl_2$ with a catalytic amount of Bu_4NBr (instead of $GeCl_2$−dioxane) gave a complicated mixture, perhaps because of expected over-reactions of tin aldolate (Table 2, entry 9).

A possible mechanism for the avoidance of over-reactions might involve the formation of halohydrin **11** from aldolate **10**, as reported by Denmark and co-workers.[19] In our case, however, NMR analysis of the reaction between **1a** and **2a** suggested no formation of halohydrin, and only germanium aldolate **10aa** was observed as the reaction intermediate (eq 6, see Supporting Information).



After a workup of **10aa** by H_2O, the ^{13}C chemical shift of the carbonyl group in **10aa** (202 ppm) moved downfield to 205 ppm (**3aa**), which indicated a weaker interaction between the carbonyl group and the germanium moiety in **10aa** than that of the hydrogen bonding in **3aa**. This observation surprised us, since a strong interaction between the carbonyl group and the germanium(IV) moiety was expected. We focused next on a detailed investigation of the Lewis acidity of germanium(IV).

First, we monitored the interaction between several Lewis acids and the formyl moiety of heptanal by ^{13}C NMR and IR (Table 6).[20] As expected, significant downfield shifts in ^{13}C NMR and a marked decrease in the carbonyl stretching frequency in the IR spectrum for a carbonyl group were observed in the interaction with $TiCl_4$ and $SnCl_4$ (entries 2

(6) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48–49.
(7) Matsubara, R.; Kawai, N.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3814–3816.

SCHEME 2. A Possible Reaction Course

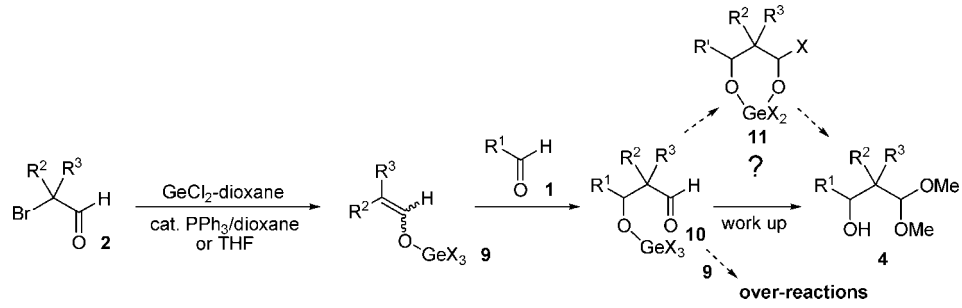
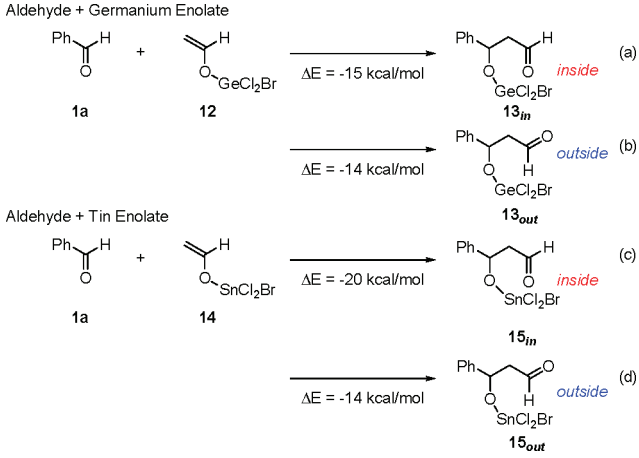


TABLE 6. Effect of Metal Halides on $\delta(^{13}C)$ or ν/cm^{-1} of Carbonyl Group in Heptanal[a]

entry	metal halide	$\delta(^{13}C)$ (ppm)	$\Delta\delta(^{13}C)$ (ppm)	ν (cm^{-1})	$\Delta\nu$ (cm^{-1})
1	none	202.61	0	1728	0
2	$TiCl_4$	219.13	+16.52	1674	−54
3	$SnCl_4$	216.89	+14.28	1668	−60
4	$GeCl_4$	201.70	−0.91	1728	0

[a] NMR, heptanal and metal halide (2.4 equiv) in $CDCl_3$. IR, heptanal and metal halide (1.0 equiv) in CCl_4.

SCHEME 3. Theoretical Calculation of Cross-Aldol Reaction of Trihalogenated Germanium/Tin Enolates 12/14 with Benzaldehyde 1a[a]



[a] Energy values are calculated values.

and 3). However, no such phenomena were observed in the case of $GeCl_4$ (entry 4). These results show that the Lewis acidity of $GeCl_4$ is quite low, as compared with $TiCl_4$ and $SnCl_4$.

Next, ab initio calculations were performed on the cross-aldol reactions to compare germanium enolate **12** and tin enolate **14** (Scheme 3).[21,22] The produced metal aldolates **13** and **15** were optimized in two situations, in which carbonyl oxygen was placed either inside ($\mathbf{13_{in}}$ or $\mathbf{15_{in}}$) or outside ($\mathbf{13_{out}}$ or $\mathbf{15_{out}}$) relative to the metal center.

The ΔE value (eq c, −20 kcal/mol) of the formation of $\mathbf{15_{in}}$ indicated a stronger interaction between the tin center and formyl oxygen than that of $\mathbf{15_{out}}$ (eq d, −14 kcal/mol). On the other hand, in the reaction of germanium enolate **12** with benzaldehyde **1a**, the formations of $\mathbf{13_{in}}$ and $\mathbf{13_{out}}$ were equally exothermic (eq a, ΔE −15 kcal/mol; eq b, ΔE −14 kcal/mol). To further clarify the nature of these metal aldolates, the optimized structures of germanium aldolates ($\mathbf{13_{in}}$, $\mathbf{13_{out}}$) and tin aldolates ($\mathbf{15_{in}}$, $\mathbf{15_{out}}$) were investigated, as shown in Figure 2.

As shown in Figure 2, the germanium center of $\mathbf{13_{in}}$ had a tetrahedral geometry similar to that of $\mathbf{13_{out}}$ ($\angle$O1GeCl1 + $\angle$Cl1GeCl2 + $\angle$Cl2GeO1: 325.4° in $\mathbf{13_{in}}$, 331.2° in $\mathbf{13_{out}}$), and similar charge values on carbonyl carbons (C3) were observed in both structures ($\mathbf{13_{in}}$, 0.49397; $\mathbf{13_{out}}$, 0.48693). In addition, germanium aldolate $\mathbf{13_{in}}$ had a significantly long Ge−O distance (Ge−O2, 4.163 Å). These results strongly suggest that the formyl group did NOT interact with the germanium center, even in $\mathbf{13_{in}}$. In contrast, a strong coordination of the carbonyl oxygen to the tin center in $\mathbf{15_{in}}$ (Figure 2c) is apparent because of a much shorter Sn−O2 distance than the Ge−O2 distance (Sn−O2, 2.379 Å) and because of the construction of a trigonal bypiramidal geometry of the tin center ($\angle$O1SnCl1 + $\angle$Cl1SnCl2 + $\angle$Cl2SnO1 = 353.1°). The coordination makes the charge of the carbonyl carbon (C3) much more positive than that of $\mathbf{15_{out}}$, which has a noncoordinated tetrahedral geometry in the tin center ($\mathbf{15_{in}}$, 0.54074; $\mathbf{15_{out}}$, 0.48802). Apparently, tin aldolate $\mathbf{15_{in}}$ is more electrophilic than $\mathbf{15_{out}}$, and this is probably the reason for the over-reactions. In contrast, germanium aldolate **13** does not take a coordinated model *regardless of the direction of the carbonyl group*, and thus, the carbonyl group is not activated.

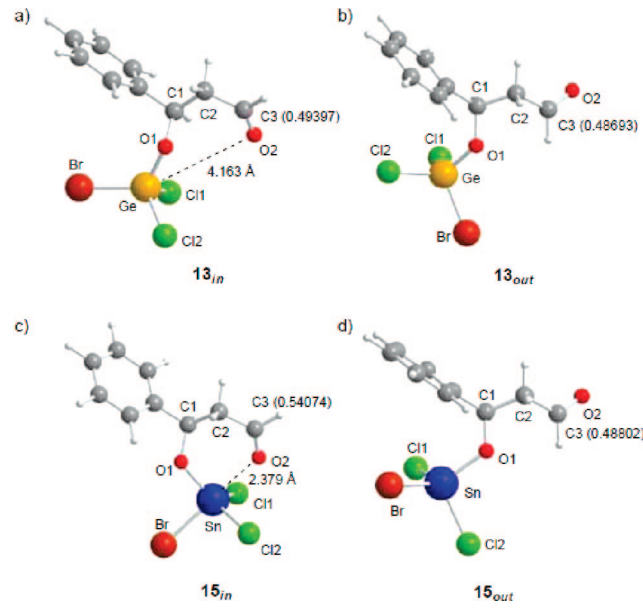


FIGURE 2. Optimized structures of germanium aldolates (a, $\mathbf{13_{in}}$; b, $\mathbf{13_{out}}$) and tin aldolates (c, $\mathbf{15_{in}}$; d, $\mathbf{15_{out}}$). Selected bond distances (Å) and NBO charges: [$\mathbf{13_{in}}$] Ge−O1, 1.767; Ge−O2, 4.163; Ge−Cl1, 2.153; Ge−Cl2, 2.145; Ge−Br, 2.296; C3, 0.49397. [$\mathbf{13_{out}}$] Ge−O1, 1.771; Ge−Cl1, 2.155; Ge−Cl2, 2.147; Ge−Br, 2.286; C3, 0.48693. [$\mathbf{15_{in}}$] Sn−O1, 2.380; Sn−O2, 2.379; Sn−Cl1, 2.366; Sn−Cl2, 2.367; Sn−Br, 2.518; C3, 0.54074. [$\mathbf{15_{out}}$] Sn−O1, 1.984; Sn−Cl1, 2.353; Sn−Cl2, 2.347; Sn−Br, 2.471; C3, 0.48802.

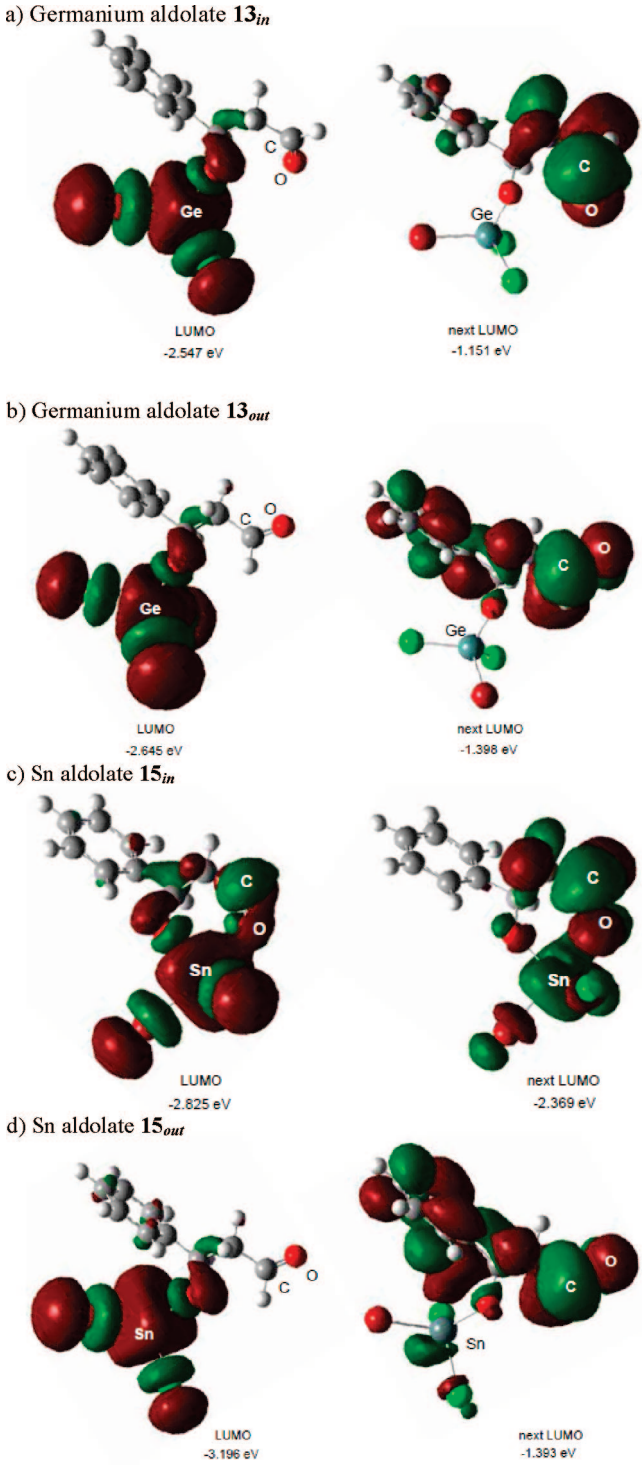
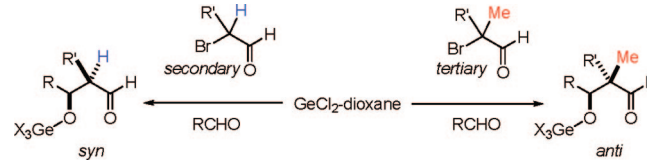


FIGURE 3. LUMOs and next LUMOs for germanium and tin aldolates: (a) $\mathbf{13}_{in}$, (b) $\mathbf{13}_{out}$, (c) $\mathbf{15}_{in}$, (d) $\mathbf{15}_{out}$.

Figure 3 displays the MO diagrams (LUMO and the next LUMO) and the energy values of the germanium and tin aldolates. For tin aldolates **15**, while the LUMO of $\mathbf{15}_{out}$ is dominated by orbitals of the tin atom (Figure 3d), the coordination model $\mathbf{15}_{in}$ has the carbonyl π^* orbital in the LUMO, which is at a very low energy level (Figure 3c, −2.825 eV). On the other hand, the LUMOs of both germanium aldolates $\mathbf{13}_{in}$ and $\mathbf{13}_{out}$ are not on the corresponding carbonyl groups (Figures 3a and b). The carbonyl π^* orbitals are involved in the next LUMOs, which are both at quite high energy ($\mathbf{13}_{in}$, −1.151 eV; $\mathbf{13}_{out}$, −1.398 eV). The energy values mean that there is significantly low reactivity of the formyl group in germanium aldolate **13**.

SCHEME 4



These NMR studies and ab initio calculations suggest that the formyl group of germanium(IV) aldolate **13** does not take a coordinated model, due to the remarkably low Lewis acidity of germanium(IV). Therefore, the formyl group of germanium(IV) aldolate **13** is NOT activated by the germanium(IV) moiety. This result is in marked contrast to that with tin(IV) aldolates, in which the carbonyl group is highly activated by the tin(IV) moiety. The unique character of germanium makes possible an efficient system for the cross-aldol reaction between aldehydes, with no undesired over-reactions. The other important point is that the resulting germanium aldolates were more sterically hindered than the starting aldehydes in most cases. The steric difference avoids over reactions well because the present system was quite sensitive to the steric environment. In fact, the substrate **1i** showed lower reactivity (Table 3, entry 14), and Bu^{t}CHO did not give the product. This situation enabled the present system to be successful without contamination of over-reaction products.

5. Change in Stereoselectivity. As noted in Tables 3 and 5, the syn-selective cross-aldol reaction using secondary α-bromoaldehydes is in sharp contrast to the anti predominance of tertiary α-bromoaldehydes (Scheme 4). To explain the interesting change in selectivity, open transition models[23] are strongly

(8) (a) Mahrwald, R.; Costisella, B.; Gündogan, B. *Tetrahedron Lett.* **1997**, *38*, 4543–4544. (b) Mahrwald, R.; Costisella, B.; Gündogan, B. *Synthesis* **1998**, 262–264. (c) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799. (d) Córdova, A. *Tetrahedron Lett.* **2004**, *45*, 3949–3952. (e) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152–2154. (f) Mase, N.; Tanaka, F.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2004**, *43*, 2420–2423. (g) Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2004**, *6*, 3541–3544. (h) Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6722–6724. (i) Wang, W.; Li, H.; Wang, J. *Tetrahedron Lett.* **2005**, *46*, 5077–5079. (j) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5527–5529. (k) Kano, T.; Yamaguchi, Y.; Tanaka, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1738–1740. (l) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2082–2084.

(9) For pioneering work on low-valent germanium-mediated reductive C−C bond formations, see:(a) Hashimoto, Y.; Kagoshima, H.; Saigo, K. *Tetrahedron Lett.* **1994**, *35*, 4805–4808. (b) Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org. Chem.* **1998**, *63*, 691–697.

(10) (a) Yasuda, M.; Tanaka, S.-y.; Baba, A. *Org. Lett.* **2005**, *7*, 1845–1848. (b) Tanaka, S.-y.; Yasuda, M.; Baba, A. *Synlett* **2007**, 1720–1724.

(11) The reductive cross-aldol reactions between aldehydes, not concerned with stereoselectivity or giving moderate selectivity, have been reported. (a) Kato, J.; Mukaiyama, T. *Chem. Lett.* **1983**, 1727–1728. (b) Maeda, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 4558–4560.

(12) Unfortunately, the reaction with tertiary aldehyde (pivalaldehyde) gave a complicated mixture.

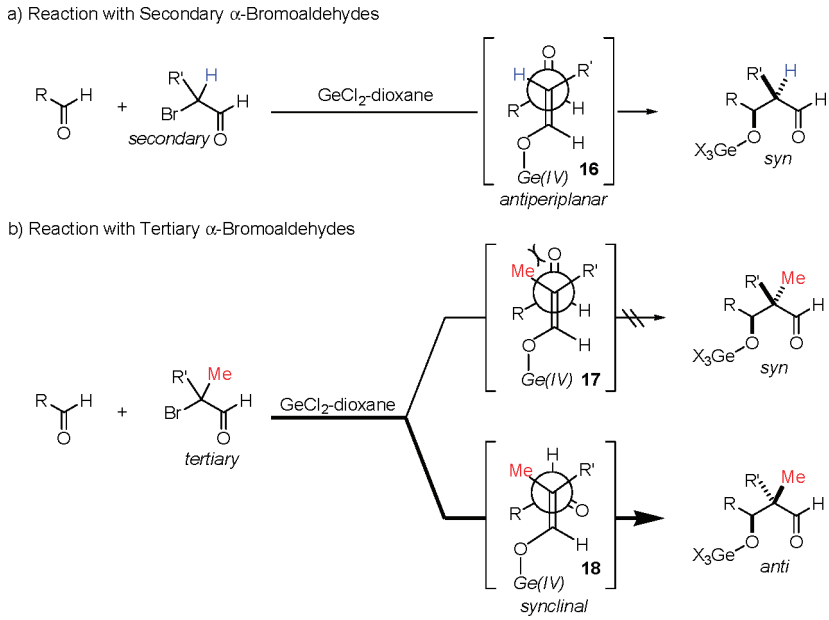
(13) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P.-J. *J. Am. Chem. Soc.* **1991**, *113*, 8036–8045.

(14) Bellesia, F.; Ghelfi, F.; Grandi, R.; Pagnoni, U. M. *J. Chem. Res. (S)* **1986**, 428–429.

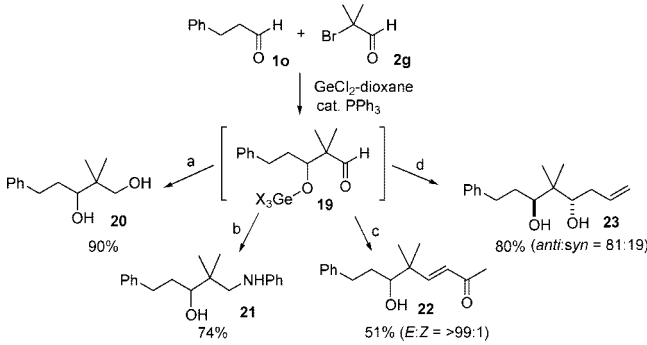
(15) For recent examples of the cross-aldol reaction concerned with the diastereoselective construction of the quaternary carbon center, see: (a) Burke, E. D.; Gleason, J. L. *Org. Lett.* **2004**, *6*, 405–407. (b) Keränen, M. D.; Eilbracht, P. *Org. Biomol. Chem.* **2004**, *2*, 1688–1690. (c) Adhikari, S.; Caille, S.; Hanbauer, M.; Ngo, V. X.; Overman, L. E. *Org. Lett.* **2005**, *7*, 2795–2797. (see also ref 8f and 8i)

(16) Unfortunately, secondary aliphatic aldehydes gave no cross-aldol products.

SCHEME 5. Open Transition State Models



SCHEME 6. One-Pot Conversion of Germanium Aldolate 7og[a]



[a] Reagents and conditions: (a) $LiAlH_4$, rt, 1 h; (b) aniline, Bu_2SnHCl, HMPA; (c) $CH_3COCHPPh_3$, 60 °C, 24 h; (d) allyltrimethylsilane, $TiCl_4$, rt, 30 min.

invoked as the transition state model, since the carbonyl oxygen−metal interacted cyclic transition model seems to be difficult owing to the low Lewis acidity of germanium(IV).

Possible open transition state models are shown in Scheme 5. When secondary α-bromoaldehydes are used, the syn selectivity can be rationalized by the antiperiplanar model **16** (Scheme 5a). In the case of tertiary bromoaldehydes, however, the synclinal transition model **18**[24] would be more favorable than the antiperiplanar model **17** (Scheme 5b), because of the minimization of an unfavorable steric interaction between the aldehyde oxygen and the methyl group (the order of steric hindrance; C_{sp3} > C_{sp2} > H). In an interesting finding, the diastereoselectivity was dramatically changed from syn to anti when tertiary α-bromoaldehydes were used instead of secondary ones.

6. One-Pot Transformation of Germanium Aldolates. After achieving the effective formation of germanium aldolate, the next objective is the successive transformation of the resulting formyl moiety (Schemes 6 and 7).[25] This one-pot methodology makes possible effective routes for multifunctionalized compounds without isolation and purification of aldol products.

Germanium aldolate **19**, generated from **1o** and **2g**, was treated with $LiAlH_4$ to give diol **20** in high yield (eq a). A reductive amination[26] provided the aminoalcohol **21** in 74% yield (eq b). A Wittig reaction proceeded stereoselectively to give only *Z*-isomer **22** (eq c). The one-pot methodology can be applied to Hosomi−Sakurai allylation[27] to give 1,3-*anti* diol **23** (eq d). Generally, the Lewis acid promoted allylation of aldol (β-hydroxyaldehyde) requires the protection of the hydroxy group.[28] In our method, fortunately, the trihalogenated germanium group acts as a temporary protecting group.

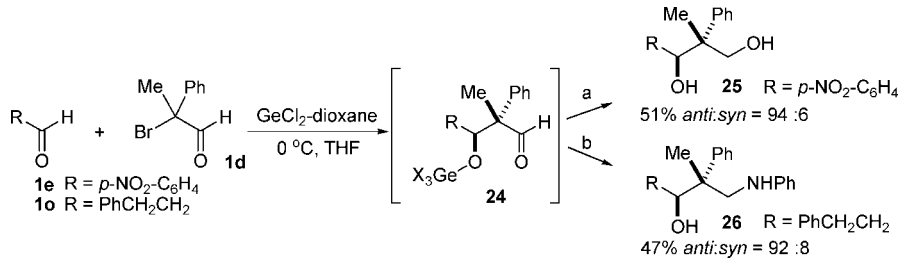
A similar one-pot methodology was applied to the reduction and reductive amination of aldolate **24** to give 1,3-diol **25** and 1,3-amino alcohol **26** with a diastereocontrolled quaternary carbon center (Scheme 7).

Conclusion

In summary, we demonstrated the Ge(II)-mediated reductive cross-aldol reaction of α-bromoaldehydes with aldehydes, in which a sharp change in stereochemistry was accomplished; secondary α-bromoaldehydes gave syn aldol products, while anti selectivities were obtained from tertiary ones. The synthetic utility of the produced germanium aldolates was demonstrated by one-pot transformations to other functionalized products. NMR study revealed the formation of several kinds of trihalogenated germanium enolates from α-bromoaldehyde and $GeCl_2$−dioxane. Furthermore, treatment with *tert*-butylpyridine gave the *tert*-butylpyridine complex of germanium enolate, which was analyzed by X-ray crystallography. Ab initio calculations revealed that the formyl moiety of the produced germanium aldolate is not activated by the germanium(IV) moiety. This unique characteristic makes possible a highly reliable method for the cross-aldol reaction of various bromoaldehydes with aldehydes, with no undesired over-reactions.

(17) Unfortunately, no cross-aldol products were obtained in the reaction of bromoaldehyde **2h** with any aldehydes.

SCHEME 7[a]



[a] Reagents and conditions: (a) $NaBH_4$, Na_2CO_3 aq; (b) aniline, Bu_2SnHCl, HMPA.

Experimental Section

Representative Procedure: Synthesis of 4gb. 2-Bromo-3-phenylpropanal **2b** (0.74 mmol) was added to a stirred suspension of 3-benzyloxypropanal **1g** (0.60 mmol), PPh_3 (0.028 mmol), and $GeCl_2$−dioxane (0.72 mmol) in dioxane (2 mL) at room temperature. After the mixture was stirred for 1 h at room temperature, methanol (8 mL) was added. The resulting solution was stirred for an additional 1 h at room temperature, and then aqueous $NaHCO_3$ (saturated; 10 mL) was added. The mixture was extracted with Et_2O/hexane (4/1, three times), dried ($MgSO_4$), and evaporated to give the crude product **4gb** (66%, syn/anti = 91:9). The crude product was purified by silica gel chromatography (hexane/EtOAc = 95/5 to 0/100) to afford the pure product **4gb** as a pale yellow liquid (0.31 mmol, 51%, syn/anti = 91:9). Data for *syn*-**4gb**: IR, (neat) 3525 (OH) cm^{-1}. ^1H NMR: (400 MHz, $CDCl_3$) 7.37−7.14 (m, 10H), 4.51 (s, 2H), 4.23 (d, J = 4.7 Hz, 1H), 4.12−4.06 (m, 1H), 3.69−3.58 (m, 2H), 3.42 (s, 3H), 3.28 (s, 3H), 3.21−3.17 (brs, 1H), 2.79 (dd, J = 14.3, 7.9 Hz, 1H), 2.72 (dd, J = 14.3, 7.1 Hz, 1H), 2.09 (dddd, J = 7.9, 7.1, 4.7, 2.0 Hz, 1H), 1.89−1.72 (m, 2H). ^{13}C NMR: (100 MHz, $CDCl_3$) 140.6, 138.2, 128.9, 128.3, 128.2, 127.6, 127.4, 125.8, 107.1, 73.1, 68.4, 68.0, 56.1, 54.2, 47.4, 33.9, 30.9; MS: (CI, 200 eV) 313 ($M^+ + 1 - MeOH$, 6), 295 ($M^+ + 1 - H_2O - MeOH$, 84), 264 (20), 263 (100), 235 (40), 191 (51), 189 (51), 173 (32), 165 (94), 161 (21), 149 (50), 148 (25), 91 (73), 75 (21). HRMS: (CI, 200 eV) calcd ($C_{20}H_{25}O_3$), 313.1804 ($M^+ + 1 - MeOH$); found, 313.1803; calcd ($C_{20}H_{23}O_2$), 295.1698 ($M^+ + 1 - H_2O - MeOH$); found, 295.1704; calcd ($C_{19}H_{21}O_2$), 281.1542 ($M^+ - 2MeOH$); found, 281.1534. Anal. Calcd for $C_{21}H_{28}O_4$ (344.4446): C, 73.23; H, 8.19. Found: C, 73.19; H, 8.18. Data for *anti*-**4gb** (selected signals are shown): ^1H NMR, (400 MHz, $CDCl_3$) 4.33 (d, J = 3.9 Hz, 1H), 3.86 (dddd, J = 8.9, 4.5, 4.5, 4.5 Hz, 1H), 3.40 (s, 3H), 3.35 (s, 3H). ^{13}C NMR: (100 MHz, $CDCl_3$) 138.2, 129.1, 125.8, 69.4, 68.7, 55.4, 47.6, 35.2, 32.0. Some signals are obscured by those of the major isomer.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of the Japanese Government. We also acknowledge financial support from the Tokuyama Science Foundation. S.T. expresses his special thanks for Research Fellowships of the Japan Society for JSPS Research Fellowships for Young Scientists.

Supporting Information Available: Experimental procedures, spectroscopic details of new compounds, listing of absolute energies and geometries for calculated species, and X-ray data for **8**, **4ee**, and disilylated compound **27** from **23** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO800904U

(18) We previously reported a remarkable effect of a bromide anion on the activation of tin enolate. Yasuda, M.; Chiba, K.; Ohigashi, N.; Katoh, Y.; Baba, A. *J. Am. Chem. Soc.* **2003**, *125*, 7291–7300. (b) Yasuda, M.; Hayashi, K.; Katoh, Y.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **1998**, *120*, 715–721. (c) Yasuda, M.; Chiba, K.; Baba, A. *J. Am. Chem. Soc.* **2000**, *122*, 7549–7555.

(19) Denmark and co-workers observed the formation of chlorohydrin in the aldol addition of trimethylsilyl enol ether to aldehyde in the presence of $SiCl_4$ (see ref 5b).

(20) (a) Power, M. B.; Bott, S. G.; Atwood, J. L.; Barron, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 3446–3451. (b) Power, M. B.; Bott, S. G.; Clark, D. L.; Atwood, J. L.; Barron, A. R. *Organometallics* **1990**, *9*, 3086–3097.

(21) All calculations were performed with Gaussian 03. The method we employed was the B3PW91 HF/DFT hybrid method. A basis set used was DGDZVP for all the atoms. Total energies for evaluation corrected with zero point energies. Solvent effects were included via a PCM model. The dielectric constant chosen was of diethyl ether, 4.335, and atomic radii with UFF referred as UA0.

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