An Activated Germanium Metal-Promoted, Highly Diastereoselective Reformatsky Reaction

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Received September 9, 1997

Activated germanium metal, prepared by the reduction of germanium(II) iodide with potassium metal, was found to promote the Reformatsky reaction effectively under mild conditions. In the presence of activated germanium metal, the reactions of α-bromo ketones **2a** and **2b** and α-bromo imides **2e** and **2f** with benzaldehyde (**1a**) proceeded smoothly to give the corresponding *β*-hydroxy carbonyl compounds **3a**, **3b**, **3e** and **3f**, respectively, in good yields and with good syn diastereoselectivity. The activated germanium metal-promoted, asymmetric Reformatsky reaction of enantiomerically pure-oxazolidinone derivatives **2g**−**j** with various aldehydes **1a**−**d** was also examined; the highest diastereoselectivity was achieved when (1*S*,2*R*)-2-amino-1,2-diphenylethanol-derived **2j** was used as the Reformatsky donor. The excellent diastereoselectivity could be explained in terms of the formation of a chairlike, six-membered transition state between the aldehyde and enolate as in the Zimmerman−Traxler model. A single recrystallization of the Reformatsky adducts, followed by hydrolysis and subsequent esterification, led to enantiomerically pure methyl 3-hydroxy-2-methylalkanoates **10j**−**m**, with almost quantitative recovery of the enantiomerically pure 2-oxazolidinone **14**.

Introduction

The Reformatsky reaction[1] employing zinc metal, an α-bromo ester, and a carbonyl compound to produce a *β*-hydroxy carboxylic ester is, along with the aldol reaction,[2] one of the most useful methods for the formation of carbon−carbon bonds. One of the advantages of the Reformatsky reaction is that the reaction proceeds under neutral conditions, in contrast with the aldol reaction which, in general, requires a base to generate the enolate or an acid to activate the electrophile. However, the yield and stereoselectivity of the Reformatsky reaction have remained at a lower level than those of the aldol reaction. This low yield and stereoselectivity of the Reformatsky reaction arise from the low reactivity of zinc metal and of the resulting Reformatsky reagent; the reaction usually has to be carried out at a high temperature, which causes concurrent undesirable side reactions and/or competitive reactions through several alternate transition states. Much effort has been made to overcome this problem, and modified procedures using a variety of other metals and certain low-valent metal species have been reported.[1d] However, the stereoselectivity of these reactions is still in general unsatisfactory, although high stereoselectivity has been achieved for a limited range of substrates.[3]

We have been interested in the reducing ability of low-valent germanium species[4] and have recently reported a germanium(II) iodide-mediated allylation reaction of carbonyl compounds (the Barbier-type allylation reaction).[5] Among group 14 elements, low-valent germanium species have only been used for a few carbon−carbon bond formation reactions,[6] and their synthetic utility still remains unclear, in contrast with tin(II) species and tin metal, which have been frequently used for carbon−carbon bond formation reactions, including for example the Reformatsky reaction.[7]

In this paper, we describe a preparative method for activated germanium metal (a low-valent germanium species) and demonstrate its successful application to the diastereoselective Reformatsky reaction.

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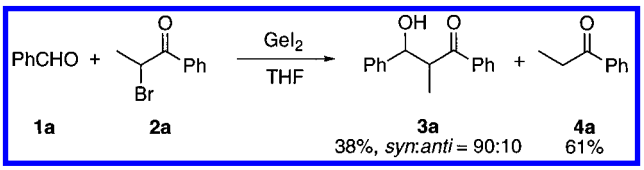
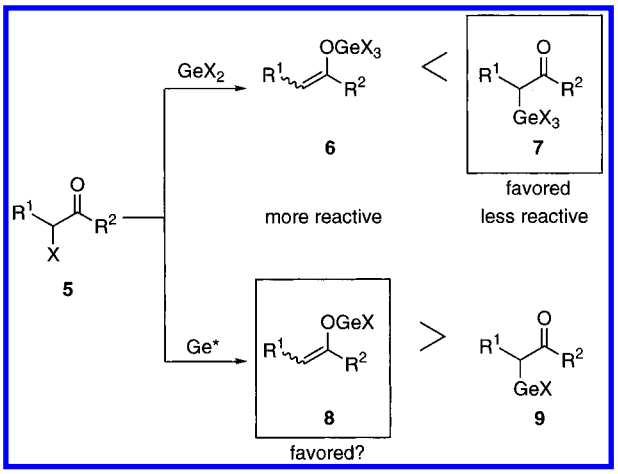
S0022-3263(97)01672-1 CCC: $15.00
Published on Web 01/22/1998

Scheme 1



Scheme 2

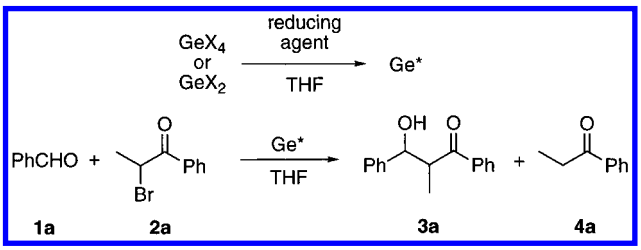


Results and Discussion

Preparation of Activated Germanium Metal. We at first used GeI_2[8] in the Reformatsky reaction of 2-bromopropiophenone (**2a**) with benzaldehyde (**1a**) (Scheme 1). However, the corresponding β-hydroxy ketone **3a** was obtained only in 38% yield, and propiophenone (**4a**), which would be produced by reduction of **2a**, was formed as the major product (61%). This result indicates that the germylated intermediate formed in situ from **2a** and GeI_2 is insufficiently nucleophilic toward the aldehyde, although the reducing power of GeI_2 is enough for it to be formed. Some low-valent germanium species (GeX_2) are known to react with α-halo carbonyl compounds **5**, giving not the germanium(IV) enolates **6** but rather the α-germyl carbonyl compounds **7** (Scheme 2).[9] Moreover, in the Reformatsky reaction using zinc metal, it is also known that metal enolates have higher reactivity than the corresponding *C*-metalated derivatives toward aldehydes.[10] This suggests the formation of a less reactive germanium(IV) intermediate from **2a** and GeI_2, such as the α-germyl carbonyl compound **7**, of which the hydrolysis results in the formation of propiophenone (**4a**) in the present reaction. Next we turned our attention to germanium metal, which can also reduce carbon−halogen bonds,[4d,11] with the expectation that germanium(II) intermediates obtained from germanium metal and α-halo carbonyl compounds may have greater ionic character than the germanium(IV) intermediates and exist preferentially in the enolate form **8**.

In screening the source of germanium metal, we chose the reaction of **2a** with **1a** as a model reaction. First, commercially available germanium powder (200 mesh, washed successively with 1 M HCl, water, and ether and then dried in vacuo) was used in this reaction. However,

Scheme 3



this germanium metal powder did not reduce **2a**, and no addition product was detected by a ^1H NMR analysis of the crude product (88% of **2a** was recovered). The low reactivity of this germanium metal powder may result from insufficient removal of metal oxide layers from the metal surface and from the low surface area of the metal particles. In general metals chemically prepared by the reduction of metal salts with alkali metals or other reducing agents are more reactive than mechanically atomized metals, and the reactivity of such activated metals is highly dependent on the conditions used in their preparation, including the starting metal salt and the reducing agent.[12] Thus, we searched for a suitable method for the preparation of activated germanium metal (Ge*), looking at various different conditions (Scheme 3). The results are summarized in Table 1.

First, germanium(IV) halides were used for the preparation of Ge*. Reduction of $GeCl_4$ with potassium metal in THF under reflux resulted in the formation of a black suspension (entry 1); the suspended Ge* was able to reduce **2a** but gave only a trace amount of **3a** (**4a** was obtained in 75% yield). In contrast, Ge*, similarly prepared from GeI_4[13] by reduction with potassium metal, promoted both reduction and addition to give **3a** in good yield (entry 2). These results indicate that iodide ion seems necessary for addition of the germanium intermediate to the aldehyde to occur. In fact by adding potassium iodide (4 equiv) to $GeCl_4$ prior to its reduction, the yield could be dramatically improved (entry 3). Although we have not yet been able to identify Ge* and the germanium intermediate produced from Ge* and **2a**, the effect of iodide ion is plausibly explained in terms of promotion of the conversion from a *C*-metalated derivative to an enolate.

Germanium(II) halides are also available sources of Ge*. Ge*, prepared by the reduction of $GeCl_2$·dioxane complex[14] with potassium metal, was again ineffective for this reaction (entry 4). In contrast, Ge*, prepared from GeI_2 by reduction with potassium metal, was highly effective in this Reformatsky reaction (entry 5); **3a** was obtained in 91% yield with good syn diastereoselectivity (94:6). Other reducing agents such as lithium metal and lithium naphthalenide were also applicable to the reduction of GeI_2. However, the reactions using such suspensions resulted in lower yield and/or lower diastereoselectivity (entries 6 and 7).

Therefore, of the germanium halide/reducing agent combinations examined, GeI_2/K was the best for the preparation of Ge* active enough for the Reformatsky reaction. Thus, we concluded that the optimal conditions

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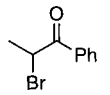
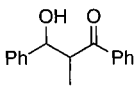
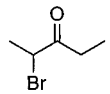
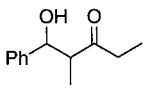
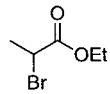
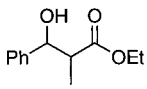
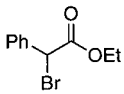
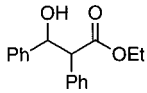
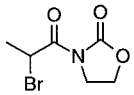
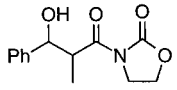
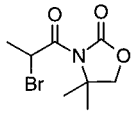
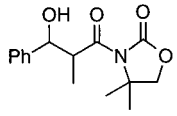
Table 1. Reactivity of Activated Germanium Metal in the Reformatsky Reaction of 2a with 1a

entry	preparation of activated germanium metal, conditions[a]	Reformatsky reaction, conditions[b]	yield (%)	syn:anti[c]
1	$GeCl_4$ (2.0), K (7.2), reflux, 2 h	rt, 72 h → reflux, 6 h	trace[d]	*e*
2	GeI_4 (2.0), K (7.2), reflux, 2 h	rt, 24 h	68	92:8
3	$GeCl_4$ (2.0), KI (4.0), K (7.2), reflux, 2 h	rt, 48 h	75	90:10
4	$GeCl_2$·dioxane (2.0), K (3.6), reflux, 2 h	rt, 72 h → reflux, 6 h	trace [f]	*e*
5	GeI_2 (2.0), K (3.6), reflux, 2 h	rt, 6 h	91	94:6
6	GeI_2 (2.0), Li (3.6), reflux, 3 h	rt, 48 h	81	77:23
7	GeI_2 (2.0), lithium naphthalenide (3.6), rt, 4 h	rt, 2 h	93	83:17

[a] Values in parentheses represent equivalents to **1a**. [b] To activated germanium metal suspended in THF were added in succession **2a** (1.2 equiv) and **1a** (1.0 equiv) at room temperature. [c] Determined on the basis of the weights of both isomers. [d] 75% of **4a** was obtained. [e] Not determined. [f] 68% of **4a** was obtained.

Table 2. Diastereoselective Reformatsky Reaction of Various α-Bromo Carbonyl Compounds 2a–f with 1a Promoted by Activated Germanium Metal[a]

entry	2-bromocarbonyl compound	reaction time (h)	product	yield (%)	*syn:anti*[b]
1	 **2a**	6	 **3a**	91	94:6[c]
2	 **2b**	48	 **3b**	90	87:13
3	 **2c**	72	 **3c**	0	——
4	 **2d**	72	 **3d**	32[d]	78:22[c]
5	 **2e**	72	 **3e**	98[e,f]	82:18
6	 **2f**	72	 **3f**	93[e,g]	85:15

[a] Activated germanium metal was prepared according to the method described in Table 1, entry 5. Molar ratio **1a**:**2**:Ge* = 1:1.2:1.8. The reaction was carried out at rt. [b] Determined by ^{1}H NMR. [c] Determined on the basis of the weights of both isomers. [d] 49% of **4d** was obtained. [e] 1.8 equiv of **2** was used. [f] 13% of **4e** was obtained. [g] 5% of **4f** was obtained.

for the preparation of Ge* were those in Table 1, entry 5, and used these in subsequent experiments.

Diastereoselective Reformatsky Reaction of α-Bromo Carbonyl Compounds with Benzaldehyde. The Reformatsky reaction of various α-bromo carbonyl compounds **2a**–**f** with benzaldehyde (**1a**) was carried out under the optimized conditions for the preparation of Ge* (Table 1, entry 5). The results are summarized in Table 2. As a result, some features of this reaction were clarified: (1) Both aromatic and aliphatic α-bromo ketones **2a** and **2b** reacted smoothly with **1a** to give the corresponding *β*-hydroxy ketones **3a** and **3b** in good yields with good syn diastereoselectivity (entries 1 and 2). (2) Although simple α-bromo esters **2c** and **2d** were reduced by Ge*, the corresponding *β*-hydroxy esters could not be obtained in acceptable yields, probably due to the low reactivity of the germanium intermediates formed (entries 3 and 4). Taking into account the fact that zinc Reformatsky reagents derived from α-halo esters exist as *C*-metalated structures[15] while those derived from α-halo ketones exist in the enolate form,[16] the corresponding *C*-metalated esters may be formed by the reaction of **2c** and **2d** with Ge*. (3) In contrast, 2-oxazolidinone derivatives **2e** and **2f** reacted smoothly with **1a** to give the Reformatsky adducts in good yields, although a small excess amount of reagent was required in order to complete the reactions (entries 5 and 6). In these reactions, intramolecular coordination of the metal (Ge*) to the oxazolidinone carbonyl oxygen would contribute to the preferential formation of an enolate, rather than a *C*-metalated intermediate.

These observations encouraged us to develop an asymmetric Reformatsky reaction using enantiomerically pure oxazolidinone derivatives and activated germanium metal to give optically active *β*-hydroxy carboxylic acid derivatives, including *β*-hydroxy propionic acid derivatives, which are very important components for the synthesis of natural products such as macrolides and polyether antibiotics.[17]

Asymmetric Reformatsky Reaction of Enantiomerically Pure Oxazolidinone Derivatives with Various Aldehydes. A few asymmetric Reformatsky reactions of nonracemic 2-bromo carboxylic acid derivatives with achiral carbonyl compounds have been reported.[18,19] Their diastereoselectivity is, however, unsatisfactory, and further improvement is desirable. For example, the asymmetric Reformatsky reaction of (*S*)-valinol-derived 3-(2-bromopropionyl)-2-oxazolidinone with

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Scheme 4

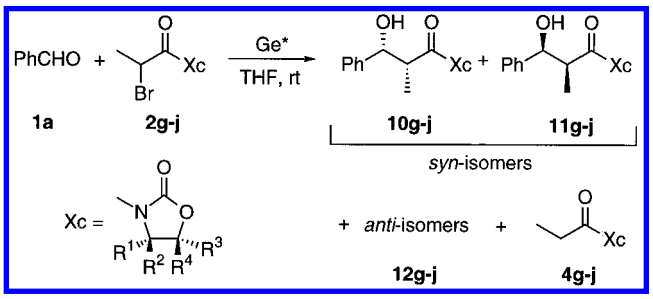

Table 3. Molar Ratio Dependence of the Reaction of 2g with 1a[a]

entry	molar ratio **1a**:**2g**[c]:Ge*	reaction time (h)	yield[d] (%)	diastereomer ratio[b] syn:anti	**10g**:**11g**
1	1:1:1	72	39	97:3	98:2
2	2:1:1	72	41[e]	97:3	98:2
3	1:1:2	72	65	97:3	99:1
4	1:1.5:1.5	72	70	99:1	99:1
5	1:2:2	18	91	97:3	98:2
6	1:2[f]:2	18	91	97:3	99:1
7	1:2[g]:2	18	90	97:3	98:2

[a] The reaction was carried out at rt. [b] Determined by GC analysis of the trimethylsilylated product. [c] A mixture of less- and more-polar diastereomers **2g** (1:1) was used. [d] Yield based on **1a**. [e] Yield based on **2g**. [f] The less-polar diastereomer of **2g** was used. [g] The more-polar diastereomer of **2g** was used.

benzaldehyde using zinc metal has been reported to give the syn and anti adducts in a ratio of almost 1:1, even though the diastereofacial selectivity for each of the adducts is moderate to excellent.[18d,e] This prompted us to apply the present activated germanium metal-promoted Reformatsky reaction, in which 2-oxazolidinone derivatives were found to be good Reformatsky donors from viewpoints of both yield and diastereoselectivity, to an asymmetric version using enantiomerically pure oxazolidinone derivatives (Scheme 4).

We first examined the optimum molar ratio of reactants for the reaction of (4*R*)-3-(2-bromopropionyl)-4-phenyl-2-oxazolidinone (**2g**)[20] with **1a** (Table 3). When equimolar amounts of **1a**, **2g**, and Ge* were employed, a mixture of the corresponding adducts **10**−**12g** was obtained in 39% yield (entry 1); the reaction proceeded with excellent diastereoselectivity, although the yield was not satisfactory. The yield was improved greatly while maintaining the excellent diastereoselectivity when excess amounts of both **2g** and Ge* were employed (entries 4 and 5), whereas increasing the molar equivalents of **1a** or Ge* was unsatisfactory (entries 2 and 3). Because of superior reaction rate, yield, and diastereoselectivity, the conditions shown in Table 3, entry 5, were applied in subsequent experiments, even though a 1 equiv excess of precious **2g** containing a chiral auxiliary had to be used and recovery of the reduced product, 3-propionyloxazolidinone **4g**, was unsatisfactory (**2g** was completely consumed).

In the preparation of oxazolidinone **2g**, racemic 2-bromopropionyl bromide was used and consequently two diastereomers of **2g** were produced (less- and more-polar diastereomers). These diastereomers were separated, and their individual reactivity and diastereoselectivity were compared with each other. No remarkable difference in yield and stereoselectivity was observed in their reactions with **1a** (entries 6 and 7), and thus we used a diastereomeric mixture as the Reformatsky donor in subsequent experiments.

Table 4. Asymmetric Reformatsky Reaction of Various 3-(2-Bromopropionyl)-2-oxazolidinones 2g−j with 1a[a]

entry	**2**, Xc =	R^1	R^2	R^3	R^4	yield (%)	diastereomer ratio[b] syn:anti	**10**:**11**
1	**2g**	H	Ph	H	H	91	97:3	98:2
2	**2h**	*i*-Pr	H	H	H	95	96:4	2:98
3	**2i**	Bn	H	H	H	91	98:2	1:99
4	**2j**	H	Ph	H	Ph	94	99:1	99:1

[a] Molar ratio **1a**:**2**:Ge* = 1:2:2. The reaction was carried out at rt for 18 h. [b] Determined by GC analysis of the trimethylsilylated product.

To discover a chiral auxiliary suitable for the construction of an effective donor in the present asymmetric Reformatsky reaction, we also prepared three kinds of 2-oxazolidinone derivative **2h**−**j**[20] from (*S*)-valinol, (*S*)-phenylalaninol, and (1*S*,2*R*)-2-amino-1,2-diphenylethanol, respectively, and carried out their reactions with **1a** (Table 4). As can be seen from Table 4, in all cases, syn/anti and diastereofacial (**10**:**11**) selectivities were quite high, and a single isomer was obtained almost pure in high yield. Here, the diastereofacial selectivities in entries 1 and 4 are the reverse of those of entries 2 and 3, a phenomenon that arises from the difference in absolute configuration at the 4-position of the oxazolidinones; those of **2g** and **2j** are *R*, whereas those of **2h** and **2i** are *S*. These results show that which diastereoface of the enolate reacts preferentially in the present reaction is decided by the configuration of the substituent at the 4-position. Of the 2-oxazolidinones examined, the (1*S*,2*R*)-2-amino-1,2-diphenylethanol-derived 2-oxazolidinone **2j** was the most effective in giving the corresponding Reformatsky adduct in good yield with excellent diastereoselectivity. This amino alcohol has several advantages as a chiral auxiliary: (1) The racemic amino alcohol can be conveniently prepared on a large scale.[21] (2) Practical and large-scale methods for the optical resolution of the racemic amino alcohol have been developed in our laboratory,[22] and both enantiomers of the amino alcohol are available. (3) Thus, the target compound having the desired absolute configuration can be obtained by correct choice of the enantiomeric amino alcohol, as we have also demonstrated for several other asymmetric reactions.[22a,23] (4) Due to the high crystallinity of the auxiliary part, the crude product can be purified by a single recrystallization to give the diastereomerically pure product.

Finally, the asymmetric Reformatsky reaction of **2j** with several aldehydes was carried out under the optimized conditions (Scheme 5, Table 5). As can be seen from Table 5,[24] excellent diastereoselectivity and moderate to good yield were achieved in all cases.

All of the adducts obtained here could be purified by a single recrystallization to give diastereomerically pure **10j**−**m**. Furthermore, these purified adducts were readily

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Scheme 5

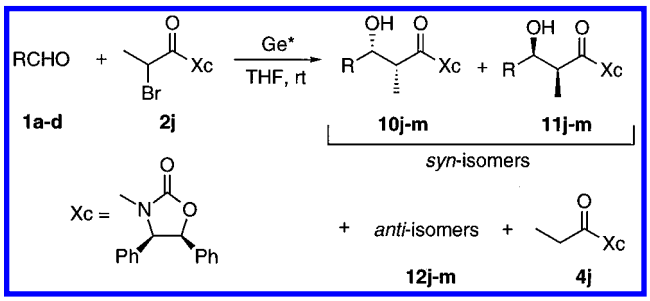

Table 5. Diastereoselective Reformatsky Reaction of 2j with Aldehydes 1a−d[a]

entry	aldehyde R		reaction time (h)	yield[c] (%)	diastereomer ratio[b] syn:anti	**10**:**11**
1	Ph	**1a**	18	94 (83)	99:1	99:1
2	*n*-Pr	**1b**	24	86 (70)	97:3	99:1
3	*i*-Pr	**1c**	24	79 (65)	95:5[d]	97:3[d]
4	(*E*)-MeCH=CH	**1d**	24	81 (66)	97:3	99:1

[a] Molar ratio **1**:**2j**:Ge* = 1:2:2. The reaction was carried out at rt. [b] Determined by GC analysis of the trimethylsilylated product. [c] The values in parentheses represent yields after recrystallization. [d] Determined by ^{1}H NMR analysis of the product.

Table 6. Conversion of the Reformatsky Adducts into Methyl Esters

entry	adduct R		methyl ester yield (%)	ee (%)	absolute configuration	**14** (%)
1	Ph	**10j**	96	>99[a]	(2*R*,3*R*)	100
2	*n*-Pr	**10k**	82	>99[b]	(2*R*,3*S*)	97
3	*i*-Pr	**10l**	83	>99[b]	(2*R*,3*S*)	97
4	(*E*)-MeCH=CH	**10m**	78	>99[b]	(2*R*,3*S*)	98

[a] Determined by HPLC analysis (Daicel Chiralcel OJ). [b] Determined by GC analysis (Chiraldex GT-A).

converted into the corresponding methyl esters **13j**−**m** by hydrolysis with lithium hydroperoxide,[27] followed by esterification with diazomethane, and the 2-oxazolidinone **14** was recovered in high yield (Table 6).

No attempt has been made to determine the enolate geometry and the oxidation state of the germanium species in the present reactions. However, on the basis of the absolute configuration of the major products, diastereofacial selection is considered to occur in the same manner as in the aldol reaction of boron enolates derived from enantiomerically pure 2-oxazolidinones.[25,28] Thus the observed syn/anti selectivity of the present Reformatsky reaction can be interpreted in terms of the Zimmerman−Traxler model,[29] in which the geometry of enolates correlates with the relative configuration of products. Furthermore, the diastereofacial selectivity achieved can be explained on the basis of a noninternally chelated enolate (Scheme 6). That is to say, reduction of **2j** with germanium metal occurs through coordination modes **15** and **16**, in which the germanium metal interacts with both the carbonyl oxygen and bromine atoms. Here, taking into account the steric repulsion in the alternative coordination modes, **15** should be highly preferred over **16**, leading preferentially to *Z*-enolate **17** as well-known Lewis acid enolates. The aldehyde approaches from the less hindered face of the *Z*-enolate **17** to form a chairlike, six-membered cyclic transition state **18**. In this transition state, the R group of the aldehyde is positioned in the quasi equatorial position, and the C=O bond of the oxazolidinone ring is located at anti to the C−O bond of the enolate.

Conclusion

In this paper, we have described (1) a method for the preparation of activated germanium metal, (2) application of activated germanium metal to the Reformatsky reaction, and (3) an asymmetric version of the reaction using (1*S*,2*R*)-2-amino-1,2-diphenylethanol as a chiral auxiliary.

Activated germanium metal, prepared by the reduction of germanium(II) iodide with potassium metal, effectively promoted the Reformatsky reaction of α-bromo ketones and α-bromo imides with aldehydes. In this way, β-hydroxy carbonyl compounds were obtained in good yields with good syn selectivity. The asymmetric Reformatsky reaction of enantiomerically pure oxazolidinone derivatives with various aldehydes also proceeded very smoothly using the activated germanium metal. Of the amino alcohols examined, (1*S*,2*R*)-2-amino-1,2-diphenylethanol was found to be the most effective chiral auxiliary. As a result, the corresponding Reformatsky adducts were obtained in good yields with both high syn/anti and diastereofacial selectivities under mild conditions.

Experimental Section

General. Where appropriate, the starting materials and reagents, purchased from commercial suppliers, were purified prior to use. The reaction flasks were flame-dried under a stream of argon. Flash chromatography was carried out using silica gel 60 (70−230 mesh ASTM). ^{1}H NMR spectra were recorded on a FT NMR instrument at 270 MHz using tetramethylsilane as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Analytical GC was performed using a 25 m methylsilicone column or a 30 m cyclodextrin column (Chiraldex GT-A). Analytical HPLC was performed using a Daicel Chiralcel OJ column with the detector wavelength at 254 nm.

(4*R*,5*S*)-3-(2-Bromopropionyl)-4,5-diphenyl-2-oxazolidinone (2j). The title compound was prepared according to the literature procedure[20] for the synthesis of analogous 3-(2-bromopropionyl)-2-oxazolidinones. To a solution of (4*R*,5*S*)-4,5-diphenyl-2-oxazolidinone[30] (4.79 g, 20.0 mmol) in THF (130 mL) was added 1.59 M *n*-BuLi in hexane (13.2 mL, 21.0 mmol) at 0 °C. After being stirred for 15 min, the solution was treated with 2-bromopropionyl bromide (2.1 mL, 20.0 mmol) at 0 °C, and the mixture was stirred for 1 h at this temperature. The reaction was quenched with saturated aqueous KH_2PO_4 solution (30 mL), and the resultant mixture was extracted with AcOEt (3 × 20 mL). The combined AcOEt extracts were dried

(24) Diastereomer ratios were determined by GC analysis of trimethylsilylated products[25] or by ^{1}H NMR analysis. For comparisons, mixtures of the adducts were independently prepared according to the methods in the literature.[26] Assignment of syn and anti configurations was based on the ^{1}H NMR vicinal coupling constants; J_{2-3} = 2−4 Hz for syn isomers and J_{2-3} = 7−9 Hz for anti isomers.

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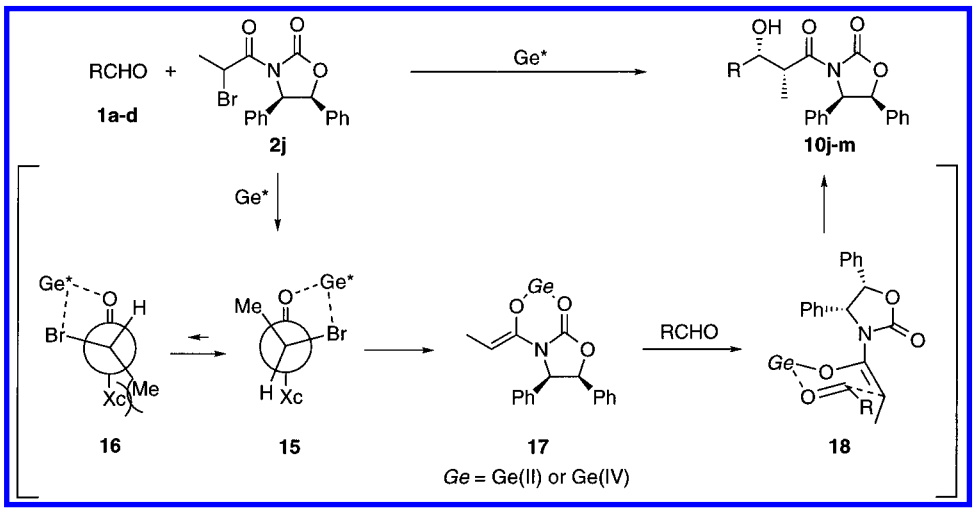
Scheme 6



over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/CH_2Cl_2 = 3/2) to give the less-polar isomer (2.51 g, 34%) and the more-polar isomer (4.53 g, 61%), respectively, as colorless crystals.

An aliquot of the less-polar isomer was recrystallized from hexane/AcOEt (5/1) to give an analytical sample. Colorless crystals: mp 127 °C; $[\alpha]^{19}_D$ +10.9 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.2−6.8 (m, 10H), 5.99 (d, 1H, *J* = 7.6 Hz), 5.84 (q, 1H, *J* = 6.8 Hz), 5.66 (d, 1H, *J* = 7.6 Hz), 1.81 (d, 3H, *J* = 6.8 Hz); IR (KBr) 1785, 1705 cm^{-1}; MS (EI, 70 eV) *m*/*z* 375, 373. Anal. Calcd for $C_{18}H_{16}NBrO_3$: C, 57.77; H, 4.31; N, 3.74. Found: C, 57.77; H, 4.28; N, 3.69.

An aliquot of the more-polar isomer was recrystallized from hexane/AcOEt (3/1) to give an analytical sample. Colorless crystals: mp 123 °C; $[\alpha]^{19}_D$ +28.6 (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.2−6.9 (m, 10H), 5.92 (d, 1H, *J* = 7.9 Hz), 5.79 (q, 1H, *J* = 6.6 Hz), 5.72 (d, 1H, *J* = 7.9 Hz), 1.84 (d, 3H, *J* = 6.6 Hz); IR (KBr) 1800, 1720 cm^{-1}; MS (EI, 70 eV) *m*/*z* 375, 373. Anal. Calcd for $C_{18}H_{16}NBrO_3$: C, 57.77; H, 4.31; N, 3.74. Found: C, 57.52; H, 4.26; N, 3.69.

General Procedure for the Asymmetric Reformatsky Reaction. To a yellow suspension of GeI_2[8] (718 mg, 2.20 mmol), which had been predried at 100 °C for 1 h under reduced pressure, in THF (4 mL) was added freshly cut potassium metal (156 mg, 4.00 mmol), and the mixture was vigorously stirred for 2 h under reflux. The resulting black suspension was allowed to cool to room temperature. To this suspension of activated germanium metal in THF were successively added dropwise **2** (2.00 mmol) in THF (4 mL) and the aldehyde (1.00 mmol) in THF (2 mL). The resulting mixture was stirred under the conditions listed in Table 5. The reaction was quenched with water (2 mL), and the volatiles were evaporated. The resultant suspension in water was filtered through a small pad of Celite and washed with CH_2Cl_2 (3 × 5 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the corresponding crude product.

(4*R*)-3-[(2*R*,3*R*)-3-Hydroxy-2-methyl-3-phenylpropionyl]-4-phenyl-2-oxazolidinone (10g). Column chromatography (CH_2Cl_2) of the crude product gave a mixture of diastereomers **10**−**12g** (91% based on the amount of **1a**) and **4g** (19% based on the amount of **2g**). The diastereomer ratio was determined by GC analysis (column temperature; 230 °C) of the trimethylsilylated adducts (syn:anti = 97:3, **10g**:**11g** = 98:2) (**10g**, 23.9 min; **11g**, 26.2 min; anti isomers, 23.6 and 29.0 min). Recrystallization (hexane/AcOEt = 3/1) of the diastereomer mixture gave **10g** in 80% recovery. Colorless crystals: mp 119−120 °C; $[\alpha]^{19}_D$ −47.9 (*c* 1.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.5−7.2 (m, 10H), 5.36 (dd, 1H, *J* = 3.6 and 8.9 Hz), 5.08 (t, 1H, *J* = 3.1 Hz), 4.57 (t, 1H, *J* = 8.9 Hz), 4.21 (dd, 1H, *J* = 3.6 and 8.9 Hz), 4.13 (dq, 1H, *J* = 3.6 and 6.9 Hz), 3.05 (d, 1H, *J* = 2.6 Hz), 1.12 (d, 3H, *J* = 6.9 Hz); IR (KBr) 3480, 1775, 1675 cm^{-1}; MS (EI, 70 eV) *m*/*z* 325 (M^+), 219 (M^+ − PhCHO). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.88; N, 4.30. Found: C, 70.02; H, 6.05; N, 4.43.

(4*R*,5*S*)-3-[(2*R*,3*R*)-3-Hydroxy-2-methyl-3-phenylpropionyl]-4,5-diphenyl-2-oxazolidinone (10j). Column chromatography (CH_2Cl_2) of the crude product gave a mixture of diastereomers **10**−**12j** (94% based on the amount of **1a**) and **4j** (22% based on the amount of **2j**). The diastereomer ratio was determined by GC analysis (column temperature; 250 °C) of the trimethylsilylated adducts (syn:anti = 99:1, **10j**:**11j** = 99:1) (**10j**, 40.6 min; **11j**, 47.4 min; anti isomers, 39.8 and 52.7 min). Recrystallization (hexane/AcOEt = 3/1) of the diastereomer mixture gave **10j** in 83% recovery. Colorless crystals: mp 155 °C; $[\alpha]^{19}_D$ +45.3 (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.5−6.8 (m, 15H), 5.74 (d, 1H, *J* = 7.6 Hz), 5.58 (d, 1H, *J* = 7.6 Hz), 5.12 (dd, 1H, *J* = 2.6 and 4.0 Hz), 4.20 (dq, 1H, *J* = 4.0 and 6.9 Hz), 3.04 (d, 1H, *J* = 2.6 Hz), 1.22 (d, 3H, *J* = 6.9 Hz); IR (KBr) 3500, 1780, 1705 cm^{-1}; MS (EI, 70 eV) *m*/*z* 401 (M^+), 295 (M^+ − PhCHO). Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.80; H, 5.77; N, 3.49. Found: C, 74.62; H, 5.87; N, 3.48.

(4*R*,5*S*)-3-[(2*R*,3*S*)-3-Hydroxy-2-methylhexanoyl]-4,5-diphenyl-2-oxazolidinone (10k). Column chromatography (CH_2Cl_2) of the crude product gave a mixture of diastereomers **10**−**12k** (86% based on the amount of **1b**) and **4j** (25% based on the amount of **2j**). The diastereomer ratio was determined by GC analysis (column temperature; 100 °C to 250 °C at 10 °C/min) of the trimethylsilylated adducts (syn:anti = 97:3, **10k**:**11k** = 99:1) (**10k**, 31.8 min; **11k**, 33.7 min; anti isomers, 30.2 and 32.9 min). Recrystallization (hexane/AcOEt = 10/1) of the diastereomer mixture gave **10k** in 70% recovery. Colorless crystals: mp 113−114 °C; $[\alpha]^{17}_D$ +35.6 (*c* 1.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.2−6.8 (m, 10H), 5.92 (d, 1H, *J* = 7.6 Hz), 5.69 (d, 1H, *J* = 7.6 Hz), 4.00 (m, 1H), 3.86 (dq, 1H, *J* = 2.6 and 6.9 Hz), 2.81 (d, 1H, *J* = 3.0 Hz), 1.6−1.3 (m, 4H), 1.25 (d, 3H, *J* = 6.9 Hz), 0.96 (t, 3H, *J* = 6.9 Hz); IR (KBr) 3450, 1790, 1685 cm^{-1}; MS (EI, 70 eV) *m*/*z* 349 (M^+ − 18). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.12; H, 6.91; N, 3.97.

(4*R*,5*S*)-3-[(2*R*,3*S*)-3-Hydroxy-2,4-dimethylpentanoyl]-4,5-diphenyl-2-oxazolidinone (10l). Column chromatography (CH_2Cl_2) of the crude product gave a mixture of diastereomers **10**−**12l** (79% based on the amount of **1c**) and **4j** (22% based on the amount of **2j**). The diastereomer ratio was determined on the basis of ^{1}H NMR integration of the hydroxy group protons (syn:anti = 95:5, **10l**:**11l** = 97:3) [**10l**, δ 2.84 (d, *J* = 3.3 Hz); **11l**, δ 2.45 (d, *J* = 3.3 Hz); anti isomers, δ 2.60 (d, *J* = 9.6 Hz) and 2.50 (d, *J* = 7.9 Hz)]. Recrystallization (hexane/ether = 10/1) of the diastereomer mixture gave **10l** in 65% recovery. Colorless crystals: mp 137 °C; $[\alpha]^{19}_D$ +46.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.2−6.8 (m, 10H), 5.92 (d, 1H, *J* = 7.8 Hz), 5.69 (d, 1H, *J* = 7.8 Hz), 4.07 (dq, 1H, *J* =

2.6 and 6.9 Hz), 3.59 (dt, 1H, J = 2.6 and 8.6 Hz), 2.84 (d, 1H, J = 3.3 Hz), 1.75 (m, 1H), 1.23 (d, 3H, J = 6.9 Hz), 1.05 (d, 3H, J = 6.6 Hz), 0.95 (d, 3H, J = 6.6 Hz); IR (KBr) 3470, 1780, 1710 cm^{-1}; MS (EI, 70 eV) m/z 295 (M^+ − *i*-PrCHO). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.88; H, 6.90; N, 3.80.

(4*R*,5*S*)-3-[(2*R*,3*S*,4*E*)-3-Hydroxy-2-methyl-4-hexenoyl]-4,5-diphenyl-2-oxazolidinone (10m). Column chromatography (CH_2Cl_2) of the crude product gave a mixture of diastereomers **10**−**12m** (81% based on the amount of **1d**) and **4j** (25% based on the amount of **2j**). The diastereomer ratio was determined by GC analysis (column temperature; 100 °C to 250 °C at 10 °C/min) of the trimethylsilylated adducts (syn: anti = 97:3, **10m**:**11m** = 99:1) (**10m**, 30.4 min; **11m**, 33.4 min; anti isomers, 29.5 and 32.9 min). Recrystallization (hexane/AcOEt = 5/1) of the diastereomer mixture gave **10m** in 66% recovery. Colorless crystals: mp 126 °C; $[\alpha]^{19}_D$ +34.0 (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.2−6.8 (m, 10H), 5.91 (d, 1H, J = 7.8 Hz), 5.79 (dq, 1H, J = 6.4 and 15.3 Hz), 5.69 (d, 1H, J = 7.8 Hz), 5.54 (dd, 1H, J = 6.4 and 15.3 Hz), 4.46 (m, 1H), 3.96 (dq, 1H, J = 3.6 and 6.9 Hz), 2.72 (d, 1H, J = 2.6 Hz), 1.73 (d, 3H, J = 6.4 Hz), 1.23 (d, 3H, J = 6.9 Hz); IR (KBr) 3450, 1795, 1680 cm^{-1}; MS (EI, 70 eV) m/z 295 (M^+ − MeCH=CHCHO). Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.45; H, 6.35; N, 3.77.

General Procedure for Removal of the Oxazolidinone Moiety.[27] To a solution of the purified Reformatsky adducts (0.45 mmol) in THF/H_2O (3/1, 2.5 mL) were added in succession 35% H_2O_2 (0.22 mL, 2.3 mmol) and solid LiOH·H_2O (38 mg, 0.91 mmol) at 0 °C. The resulting mixture was stirred at 0 °C until the starting material was undetectable on TLC. The reaction mixture was then treated with a 10% aqueous Na_2SO_3 solution (2 mL), and THF was removed by rotary evaporation. The aqueous residue was diluted with H_2O (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined CH_2Cl_2 extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give the recovered 2-oxazolidinone **14**. The aqueous layer was acidified with 3 M HCl (3 mL) at 0 °C and then extracted with AcOEt (3 × 5 mL). The combined AcOEt extracts were dried ($MgSO_4$) and concentrated under reduced pressure to yield the carboxylic acid. To the crude carboxylic acid was added an ethereal solution of CH_2N_2 until its yellow color persisted after vigorous stirring. After being treated with acetic acid, the solution was concentrated under reduced pressure. Purification by PTLC or column chromatography gave the pure ester.

Methyl (2*R*,3*R*)-3-hydroxy-2-methyl-3-phenylpropionate (13j): 96% yield after PTLC (hexane/AcOEt = 3/1) purification; >99% ee determined by HPLC analysis (hexane/*i*-PrOH = 15/1; 0.5 mL/min; **13j**, 23.9 min; ***ent*-13j**, 27.1 min); $[\alpha]^{19}_D$ +23.6 (*c* 2.62, $CHCl_3$) [lit.[26] $[\alpha]^{20}_D$ +23.5 (*c* 3.23, $CHCl_3$)].

Methyl (2*R*,3*S*)-3-hydroxy-2-methylhexanoate (13k): 82% yield after column chromatography (hexane/AcOEt = 5/1) purification; >99% ee determined by GC analysis (column temperature, 110 °C; **13k**, 8.0 min; ***ent*-13k**, 9.4 min); $[\alpha]^{22}_D$ −11.8 (*c* 1.16, $CHCl_3$) [lit.[26] $[\alpha]^{25.5}_D$ +12.05 (*c* 1.92, $CHCl_3$) for ***ent*-13k**; lit.[28] $[\alpha]^{25}_D$ −13.4 (*c* 1.0, CH_2Cl_2)].

Methyl (2*R*,3*S*)-3-hydroxy-2,4-dimethylpentanoate (13l): 83% yield after column chromatography (hexane/AcOEt = 5/1) purification; >99% ee determined by GC analysis (column temperature, 110 °C; **13l**, 6.7 min; ***ent*-13l**, 7.3 min); $[\alpha]^{20}_D$ +7.9 (*c* 0.84, $CHCl_3$) [lit.[26] $[\alpha]^{20}_D$ +7.50 (*c* 2.51, $CHCl_3$)].

Methyl (2*R*,3*S*,4*E*)-3-hydroxy-2-methyl-4-hexenoate (13m): 78% yield after column chromatography (hexane/AcOEt = 5/1) purification; >99% ee determined by GC analysis (column temperature, 110 °C; **13m**, 9.2 min; ***ent*-13m**, 12.2 min); $[\alpha]^{22}_D$ −11.8 (*c* 1.00, $CHCl_3$) [lit.[26] $[\alpha]^{25.5}_D$ +11.52 (*c* 0.82, $CHCl_3$) for ***ent*-13m**; lit.[28] $[\alpha]^{25}_D$ −12.3 (*c* 3.0, CH_2Cl_2)].

JO971672J