# Asymmetric Samarium-Reformatsky Reaction of Chiral α-Bromoacetyl-2-oxazolidinones with Aldehydes

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The samarium(II) iodide mediated asymmetric Reformatsky-type reaction of chiral 3-bromoacetyl-2-oxazolidinones with various aldehydes was studied. A series of chiral 4-substituted 2-oxazolidinones **1**−**3** and 5,5-disubstituted "SuperQuat" oxazolidinones **4**−**5** were employed as chiral auxiliaries of the α-bromoacetic acid. The reaction of **1** with various aldehydes gave the α-unbranched *β*-hydroxy carboximides in good yields with high diastereomeric excess values (up to >99% de). The majority of the reaction product derived from 5,5-diphenyl SuperQuat **5** were highly crystallinity; a single recrystallization yielding a diastereomerically pure product with the other diastereomer not detectable by spectroscopic methods. The absolute configurations of the *β*-hydroxy carboximides were determined by signs of optical rotations of the corresponding known ethyl esters referring to the literature values. Hydrolytic cleavage of the appended of *β*-hydroxy moieties from the auxiliary SuperQuats was readily achieved under mild conditions using lithium hydroxide; the corresponding carboxylic acids and the returned SuperQuats were obtained in good yields without any evidence of racemization. The first step of the reaction is the reduction of the α-bromo group to produce the samarium enolate, which adds to an aldehyde. The absolute configuration of the adduct (**7i**) derive from benzaldehyde was found to be *R*, with the samarium enolate favoring the transition state predicted from chelation control of the reagent; this is in analogy to the discussion that has been used for the corresponding titanium enolate. The stereochemistry of the reaction may be explained by incorporating the Nerz-Stormes−Thornton chair transition structure model.

## Introduction

The Reformatsky reaction was discovered in 1887 and has historically involved the reaction between zinc and an α-halo ester generating in situ an organozinc species; it is this organozinc reagent that reacts with the aldehyde or ketone resulting in the corresponding *β*-hydroxy ester.[1] *β*-Hydroxy esters are functional building blocks that have found many uses in, for example, natural product synthesis, and these are as a consequence highly prized, valuable intermediates especially if in an enantiomerically enriched form.

A common problem associated with the traditional protocol of using zinc dust is the lack of reactivity associated with this metal for the α-bromoester; consequently, it is often necessary to "activate" zinc via its amalgam with, for example, copper or mercury. Alternative methods are available that incorporate inorganic metals or organometallic reagents; these often circumvent the reactivity problems described and as a consequence allow the reaction to proceed in an expedient manner.[2]

Highly stereocontrolled asymmetric variants of the Reformatsky reaction are of current interest and an efficient asymmetric version of the Reformatsky reaction would be an exceedingly desirable reaction to have in the armory of the synthetic chemist. Be that as it may, very few asymmetric Reformatsky reactions are known; in contrast, the success of the asymmetric aldol reaction (the product of a Reformatsky reaction) is widely recognized and furthermore has been extensively studied.[3]

Samarium(II) iodide is known to be a highly versatile reagent, and its use in an *intramolecular* sense in an asymmetric Reformatsky reaction has already been reported.[4] There are in the literature examples of highly stereoselective organic reactions that result in enantiomerically enriched products via the use of samarium(II) iodide. Furthermore, the use of samarium(II) iodide as a chelation control element in intra- and intermolecular 1,2- and l,3-asymmetric inductions seems favorable.[5,6] We

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(1) For reviews, see: (a) Fürstner, A. *Synthesis* **1989**, 571. (b) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press: London, 1996.

(2) For examples for metal and metal salts reagents, see the following. (a) Al: Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705; *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3301. Matsubara, S.; Tsuboniwa, N.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3242. (b) Ce: Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904. Fukuzawa, S.; Tsuruta, T.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1473; Fukuzawa, S.; Hirai, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1963. (c) Cr: Dubois, J. E.; Axiotis, G.; Bertouneque, E. *Tetrahedron Lett.* **1985**, *26*, 4371. (d) Sb: Huang, Y. Z.; Cheng, C.; Shen, Y. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2855. (e) Sn: Harada, T.; Mukaiyama, T. *Chem. Lett.* **1982**, 161, 467. (f) Sm Tabuchi, T.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889. Inanaga, J.; Yokoyama, Y.; Handa, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 6371.

(3) (a) Guette, M.; Capillon, J.; Guette, J.-P. *Tetrahedron*, **1973**, 29, 3659. (b) Soai, K.; Kawase, Y. *Tetrahedron*: *Asymmetry* **1991**, *2*, 781. (c) Soai, K.; Oshio, A.; Saito, T. *Chem. Commun.* **1993**, 811. (d) Ito, Y.; Terashima, S. *Tetrahedron* **1991**, *47*, 2821. (e) Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org. Chem.* **1998**, *63*, 691.

(4) Molandar, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P.-J. *J. Am. Chem. Soc.* **1991**, *113*, 8036.

(5) For a review of samarium(II) iodide in organic synthesis, see: Molander, G. A.; Harris, C. H. *Chem. Rev.* **1996**, *96*, 307.

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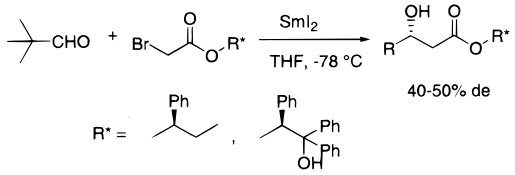
**Scheme 1**




and other research groups have reported that ketyl−alkene coupling reactions are possible with excellent diastereoselectivities using chiral auxiliaries bond esters,[7] acetals,[8] and aldehydes.[9] In this study on asymmetric synthesis incorporating samarium(II) iodide, we have only been interested in *intermolecular* asymmetric Reformatsky reactions.[10] We would like to describe in more detail the research that was undertaken and results obtained from the use of Evans' chiral 2-oxazolidinones and Davies' 5,5-disubstituted SuperQuat variants. A possible reaction mechanism is put forward that accounts for configuration of resulting aldol adducts.

## Results and Discussion

We initially tried the reaction of pivalaldehyde with chiral α-bromoacetate derived from chiral *sec*-alcohols (Scheme 1).[11] Unfortunately, the diastereoselectivity of the reaction was not satisfactory, giving a low diastereomeric excess (up to 50% de). After screening several chiral auxiliaries for α-bromoacetic acid, we directed our attention to the use of chiral 2-oxazolidinone auxiliaries as the stereochemical controlling element in the asymmetric samarium−Reformatsky reaction.[12] We then examined the stereoselectivity of the Reformatsky-type reaction of a Evans' chiral 3-(2-bromoacetyl)-2-oxazolidinone with isobutyraldehyde using a series of three 4*S*-substituted auxiliaries **1**−**3**, e.g., isopropyl, phenyl, and phenylmethyl. The reaction was usually carried out as follows. To a tetrahydrofuran (THF) solution of samarium(II) iodide (2.0 equiv) was simultaneously added the 3-(2-bromoacetyl)-2-oxazolidinone **1**−**3** (1 equiv) and an aldehyde (1.2 equiv) at −78 °C. The resulting mixture was stirred at the same temperature for 0.5 h, during which time the color of the solution turned from deep green to yellow-brown. After the usual acidic workup, the *β*-hydroxy carboximide **7** was isolated by column chromatography (Scheme 2). The diastereomeric excess (% de) of **7** was determined by GC after trifluoroacetylation and/or by HPLC in its original form. Almost the same diastereoselectivities and chemical yields were obtained in the reaction with each chiral 4-substituted 3-bromoacetyloxazolidinone auxiliary (Table 1, entries 1−3). For this reason and for ease of analysis by GC/MS, we chose **1** as the suitable chiral auxiliary for the reaction with various aldehydes. We turned our attention next to the effect, i.e., yields and de's, that different aldehydes would have on the outcome of the Reformatsky reaction using **1** (Table 1). The yields of the products were good to excellent and the de values were high for the straight chain, branched aliphatic aldehydes and aromatic aldehydes. The de value was the highest with the hindered aldehyde such as pivalaldehyde (entry 6). It is necessary for the reaction with benzaldehyde that the stepwise addition of the 3-bromoacetyloxazolidinone first and benzaldehyde afterward; this obviates the formation of pinacol as a major product and low yield of the aldol adduct.

**Scheme 2**

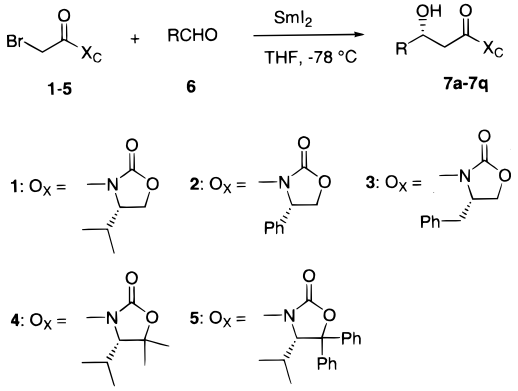



**Table 1. Reformatsky-type Reaction of α-Bromoacetyl-2-oxazolidinones 1−5 with Aldehydes[a]**

| entry | $BrCH_2COXc$ | R in aldehyde | product | %, yield[b] | %, de[c] |
|---|---|---|---|---|---|
| 1 | **1** | *i*-Pr | **7a** | 92 | 83 |
| 2 | **2** | *i*-Pr | **7b** | 88 | 80 |
| 3 | **3** | *i*-Pr | **7c** | 90 | 78 |
| 4 | **1** | $Et_2CH$ | **7d** | 95 | 76 |
| 5 | **1** | *c*-$C_6H_{11}$ | **7e** | 78 | 84 |
| 6 | **1** | *t*-Bu | **7f** | 87 | >99 |
| 7 | **1** | *n*-$C_7H_{15}$ | **7g** | 81 | 82 |
| 8 | **1** | $PhCH_2CH_2$ | **7h** | 67 | 86 |
| 9[d] | **1** | Ph | **7i** | 67 | 64 |
| 10 | **4** | *i*-Pr | **7j** | 64 | 98 |
| 11 | **4** | *t*-Bu | **7k** | 66 | >96 |
| 12 | **4** | *n*-$C_7H_{15}$ | **7l** | 55 | 94 |
| 13[d] | **4** | Ph | **7m** | 87 | 49 |
| 14 | **5** | *i*-Pr | **7n** | 32 | 90 |
| 15 | **5** | *t*-Bu | **70** | 60 | 99 |
| 16 | **5** | *n*-$C_7H_{15}$ | **7p** | 42 | 70 |
| 17[d] | **5** | Ph | **7q** | 32 | >99 |

[a] Samarium(II) iodide (2.2 mmol), **1**−**5** (1.0 mmol), aldehyde (1.0 mmol), THF (22 mL): −78 °C, 2 h. [b] Isolated yield. [c] Determined by GC/MS or HPLC. [d] Benzaldehyde was added after addition of the α-bromoacetyl-2-oxazolidinone.

Absolute configurations of the alcoholic carbon in the *β*-hydroxy carboximide **7** were determined by converting them into the corresponding ethyl esters.[13] From the sign of the optical rotations of the *β*-hydroxy ethyl esters **8** (R = Ph, *i*-Pr, *n*-$C_7H_{15}$), the stereochemistry of the alcoholic carbon in each compound was revealed to be the *R* configuration in **8a** (R = *i*-Pr) and **8g** (R = Ph) and *S* configuration in **8h** (R = *n*-$C_7H_{15}$) (Table 2).[14]

(6) (a) Kito, M.; Sakai, T.; Yamada, K.; Matsuda, F.; Shirahama, H. *Synlett* **1993**, 158. (b) Kawatsura, M.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 6900. (c) Kawatsura, M.; Hosaka, K.; Matsuda, F.; Shirahama, H. *Synlett* **1995**, 729. (d) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373. (e) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

(7) Fukuzawa, S.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, 119, 1482.

(8) Molander, G. A.; McWilliams, J. C.; Noll, B. C. *J. Am. Chem. Soc.* **1997**, 119, 1265.

(9) Taniguchi, N.; Uemura, M. *Tetrahedron Lett.* **1997**, *38*, 7199.

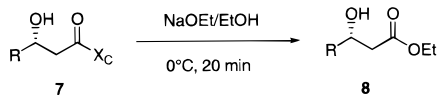
(10) For a preliminary communication, see: Fukuzawa, S.; Tatsuzawa, M.; Hirano, K. *Tetrahedron Lett.* **1998**, *39*, 6899.

(11) Chiral 1,1,2-triphenylethanediol has been reported as a useful chiral auxiliary for aldol reaction. Braun, M.; Graf, S.; Herzog, S. *Org. Synth.* **1995**, *72*, 32; 42.

(12) For a review on chiral oxazolidinones in asymmetric synthesis: Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, 96, 835−875; *Aldrichim. Acta* **1997**, *30*(1), 3.

(13) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

**Table 2. Transesterification of β-Hydroxy Carboximide (7) with Sodium Ethoxide**



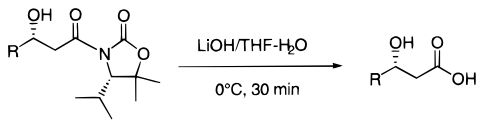

7 8

| entry | 7 | %, yield of **8** | $[\alpha]^{20}_D$ | config |
|---|---|---|---|---|
| 1 | **7a**; R = *i*-Pr | **8a**; 87 | +34.30 (*c* = 0.708, $CHCl_3$) | *R* |
| 2 | **7f**; R = *t*-Bu | **8f**; 86 | +43.48 (*c* = 1.48, $CHCl_3$) | |
| 3 | **7g**; R = $C_7H_{15}$ | **8g**; 85 | +10.43 (*c* = 1.24, $CHCl_3$) | *S* |
| 4 | **7i**; R = Ph | **8i**; 81 | +43.35 (*c* = 0.392, $CHCl_3$) | *R* |

As described above, the oxazolidinone auxiliaries **1** were revealed to be efficient for the asymmetric samarium−Reformatsky reaction by providing high stereoselectivities and chemical yields. A recent addition to the oxazolidinone auxiliary family are SuperQuats; these have been developed by Davies et al. specifically to overcome the major drawbacks that the Evans oxazolidinones have in the selective removal from the aldol products and recyclability; the endocyclic cleavage of the oxazolidinone ring often occurs in hindered carboximides during nucleophilic hydrolysis to give unwanted products.[15] The SuperQuats exhibit highly efficient *exo*cyclic cleavage properties and furthermore have the overriding advantage that they are highly crystalline in nature and in practical terms are identical to the Evans auxiliaries.[16] We employed the isopropyl SuperQuat chiral auxiliaries **4** for the samarium−Reformatsky reaction. These results are also shown in Table 1 (entries 10−13). Though the yields of the products were lower than those with **1**, stereoselectivities were higher than with **1**; the reaction with isobutyraldehyde and octanal gave 98% and 94% de, respectively, while the reaction of **1** with these aldehydes gave 78−82% de. Removal of the SuperQuat oxazolidinone moiety was easy to carry out by just treating the β-hydroxy SuperQuat with lithium hydroxide in THF/$H_2O$ for 30 min. The corresponding β-hydroxy acid **9** and the parent SuperQuat were obtained in high yields (80−90%) without racemization; the ee value of **9** was comparable with the de value in the parent β-hydroxy SuperQuat. The stereochemistry of the alcoholic carbons in **9** (**9j**; R = *i*-Pr, **9m**; R = Ph) could also be determined by the signs of their optical rotations.[17] As both of them exhibited a positive optical rotation, the *R* configurations could be assigned in **9j** (R = *i*-Pr) and in **9m** (R = Ph); the stereochemistry of **9** was in agreement with that of **8**, which was obtained from the 5-unsubstituted oxazolidinone (Table 3).

A more sterically crowded derivative of the original *gem*-dimethyl SuperQuat auxiliary has been developed, namely the *gem*-5,5-diphenyl-2-oxazolidinone (5,5-diphenyl SuperQuat).[18] We sought to incorporate this auxiliary into our samarium−Reformatsky study; again for comparison purposes, the (4*S*)-isopropyl-5,5-diphenyl-2-oxazolidinone **5** was used. Though the chemical yields were not satisfactory, the de values were almost the same as with the SuperQuat **4** (Table 1, entries 14−17), the 5,5-diphenyl SuperQuat **5** has an advantage that conveys a high degree of crystallinity to the products, which are easy to purify by a single recrystallization to give the diastereomerically pure compounds.

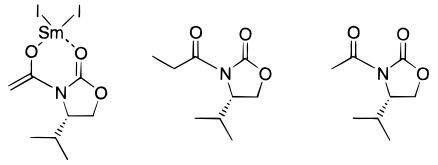
**Table 3. Hydrolysis of β-Hydroxy SuperQuat (7) with Lithium Hydroxide**




7 9

| entry | 7 | %, yield of **9** | $[\alpha]^{20}_D$ | config |
|---|---|---|---|---|
| 1 | **7j**; R = *i*-Pr | **9j**; 87 | +12.83 (*c* = 0.99, MeOH) | *R* |
| 2 | **7l**; R = *n*-$C_7H_{15}$ | **9l**; 81 | +14.57 (*c* = 1.02, $CHCl_3$) | − |
| 3 | **7m**; R = Ph | **9m**; 85 | +29.52 (*c* = 0.21, $CHCl_3$) | *R* |

**Chart 1**



10 11 12

The first step of the samarium-Reformatsky reaction should involve the reduction of the α-bromoacetyl group of **1** to give the samarium imide enolate **10**, which nucleophilically attacks the aldehyde (Chart 1). The samarium atom would then play an important role in the transition state of the reaction for high diastereoselectivity (vide infra). Chiral oxazolidinone auxiliaries are often employed for the asymmetric aldol reaction with metal (Li,[19] B,[13] Zn,[3d] Ti,[19] Ge[3e]) enolates of 3-propionyloxazolidinone **11**, where a high degree of diastereoselectivity can be achieved (over 99% de).[3d−e,13] On the other hand, the aldol reaction with the metal enolates of the acetyloxazolidinone **12** afforded low or no diastereoselectivity. For example, Evans et al. reported that the reaction of a boron enolate of **12** with isobutyraldehyde gives a mixture of diastereomers in the ratio of 52:48.[13] Thus, the α-methyl group seems to be critical for achieving a highly diastereoselective aldol reaction, including Reformatsky reaction. The α-methylthio-substituted acetyloxazolidinone may be used for the stereoselective preparation of an α-unbranched β-hydroxy carboximide after reductive removal of the methylthio group.[13] The samarium imide enolate is superior to the other metal imide enolate for directly preparing α-unbranched β-hydroxy acids or esters without any modification of the organic molecule.[19]

(14) For literature values of optical rotations: (*S*)-(**8a**; R = *i*-Pr), $[\alpha]_D = -14.3$ (*c* = 0.3, MeOH), Sugiyama, T.; Yoshikawa, M.; Yoneda, T.; Tai, A. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1089. (*R*)-(**8g**; R = $C_7H_{15}$), $[\alpha]_D = -10.0$ (*c* = 1.20, $CHCl_3$), Basile, T.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *Synthesis* **1990**, 305. (*R*)-(**8i**; R = Ph), $[\alpha]_D = +43.1$ (*c* = 3.11, $CHCl_3$), Soai, K.; Yamanoi, T.; Hikima, H.; Oyamada, H. *Chem. Commun.* **1985**, 138.

(15) Davies, S. G.; Doisneau, G. J.-M.; Prodger, J. C.; Sanganee, H. J. *Tetrahedron Lett.* **1994**, *35*, 2369.

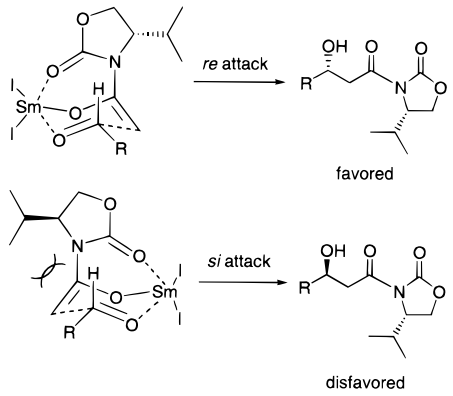
(16) (a) Davies, S. G.; Sanganee, H. J. *Tetrahedron*: *Asymmetry* **1995**, 6, 671. (b) Bull, S. D.; Davies, S. G.; Jones, S.; Polywka, M. E. C.; Prasad, R. S.; Sanganee, H. J. *Synlett* **1998**, 519.

(17) For literature values of optical rotations: (*S*)-(**9j**; R = *i*-Pr), $[\alpha]_D = -42.1$ (*c* = 1.8, $CHCl_3$); (*S*)-(**9m**; R = Ph), $[\alpha]_D = -17.1$ (*c* = 4.1, EtOH).[13]

(18) Gibson, C. L.; Gillon, K.; Cook, S. *Tetrahedron Lett.* **1998**. 39. 6733.

(19) For examples for successful asymmetric synthesis of α-unbranched β-hydroxy acids or esters, see: (a) Dongala, E. B.; Dull, D. L.; Miioskowski, C.; Soladie, G. *Tetrahedron Lett.* **1973**, 4983. (b) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381. (c) Nagao, Y.; Hagiwara, Y.; Kumagai, Y.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2393. (d) Duthaler, R. O.; Hafner, M.; Riediker. *Pure Appl. Chem.* **1990**, *62*, 631. (e) Cooke, J. W. B.; Davies, S. G.; Naylor, A. *Tetrahedron*, **1993**, *49*, 7955 and ref 10.

**Scheme 3**




Nerz-Stormes and Thornton reported that the reaction of the lithium and titanium enolates of **12** with benzaldehyde mainly gives the *S* (77% de) and *R* isomers (50% de), respectively.[20] The stereochemistry of the reaction with lithium enolate is determined by a nonchelated transition structure not coordinated to the oxazolidinone carbonyl, while the stereochemistry of the titanium enolate is predominated by chelation control, thus coordinated to the oxazolidinone carbonyl. We confirmed the stereochemistry of the samarium−Reformatsky adduct with benzaldehyde (**7i**); it is *R*, like the aldol adduct with a titanium enolate. It may be concluded that the samarium enolate strongly favors the adduct predicted by chelation control analogous to a titanium enolate.[20] Thus, the stereochemistry of the reaction may be explained by the Nerz-Stormes−Thornton chair transition structure model as shown in Scheme 3.[21] In the chelated transition state, samarium enolate disfavors a *si* face the attack on aldehyde because the isopropyl group is oriented in a sterically hindered environment. The samarium enolate then favors the less hindered *re* face attack on the aldehyde, preferably leading to the *R* alcohol isomer.

## Experimental Section

**General Methods.** $^1$H (400 MHz) and $^{13}$C NMR spectra were recorded in $CDCl_3$, and the chemical shifts are reported in $\delta$ units downfield from tetramethylsilane used as the internal standard. GC/MS analyses were carried out using a capillary column (DB-5-30N-STD, J&W Scientific, 0.25 mm, 30 m) and helium as the carrier gas. HPLC analyses were performed on a Daicel Chiralcel OD and OB columns (0.46 mm, 25 cm) eluting with 2-propanol/*n*-hexane (1/9−1/100) or a ODS (Kanto Chemicals Ltd., Mightysil RP-18) column. Elemental analyses were carried out in the Microanalytical Laboratory at Chuo University. Column chromatography was performed using Merck silica gel 60.

**Materials.** THF was freshly distilled from sodium benzophenone ketyl. 4*S*-(1-methylethyl)-, 4*R*-(1-methylethyl)-, 4*S*-(phenyl)-, and 4*S*-(phenylmethyl)-2-oxazolidinone were purchased from Aldrich Co., Inc., or prepared by the reaction of the corresponding chiral amino alcohols and diethyl carbonate. Modified chiral oxazolidinones, i.e., 4*S*-(1-methylethyl)-5,5-dimethyl-2-oxazolidinone (isopropyl SuperQuat) and 4*S*-(1-methylethyl)-5,5-diphenyl SuperQuat, were prepared by the reported method.[16,18] All of the aldehydes and ketones are commercially available and purified by distillation under reduced pressure before use.

**4*S*-3-(2-bromoacetyl)-4-(1-methylethyl)-2-oxazolidinone (1).** The following provides the typical experimental procedure for the preparation of the chiral 3-(2-bromoacetyl)-2-oxazolidinones. In a two-neck round-bottom flask containing a magnetic stirring bar were charged 4*S*-(1-methylethyl)-2-oxazolidinone (6.50 g, 50 mmol) and dry THF (200 mL) under a slight pressure of nitrogen. The flask was cooled in a dry ice−methanol bath (−78 °C), and a hexane solution of *n*-BuLi (1.6 M, 35 mL, 55 mmol) was then added using a syringe through the septum with magnetic stirring. After 30 min, bromoacetyl chloride (8.00 g, 51 mmol) was slowly added to the mixture at the same temperature over a period of 20 min. When the addition was completed, the dry ice bath was removed, and the mixture was allowed to warm to room temperature and stirred for an additional 1 h. The reaction was quenched with saturated aqueous potassium hydrogen phosphate (50 mL), and the solution was then extracted with three 50 mL portions of diethyl ether. The combined extracts were dried over $MgSO_4$, and the solvent was removed on a rotary evaporator leaving an orange liquid. The crude product was purified by column chromatography on silica gel with hexane/ethyl acetate = 3:1 as the eluent to give a pale yellow solid (10.0 g, 40 mmol, 80% yield): pale yellow solid; mp 45−47 °C; $[\alpha]^{20}_D = +66.35$ ($c = 1.037$, $CHCl_3$); $^1$H NMR ($CDCl_3$,-400 MHz) $\delta$ 0.91 (d, 3H, $J = 7.0$ Hz), 0.94 (d, 3H, $J = 7.0$ Hz), 2.42 (sept d, 1H, $J = 3.2$, 7.0 Hz), 4.28 (dd, 1H, $J = 3.2$, 9.0 Hz), 4.36 (dd, 1H, $J = 8.3$, 9.0 Hz), 4.46 (m, 1H), 4.42 (d, 1H, $J = 12.1$ Hz), 4.60 (d, 1H, $J = 12.1$ Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.4, 14.5, 18.6, 27.8, 58.4, 63.9, 153.3, 165.7; IR (KBr) 1776, 1695 ($\nu_{C=O}$). Anal. Calcd for $C_8H_{12}BrNO_3$: C, 38.42; H, 4.84; N, 5.60. Found: C, 38.16; H, 4.79; N, 5.42.

**Samarium(II) Iodide Mediated Reformatsky-Type Reaction.** All reactions were carried out in a nitrogen atmosphere using a Schlenk tube with standard techniques for air-sensitive materials. The following description provides a typical experimental procedure for the Reformatsky-type reaction of a chiral 3-bromoacetyl-2-oxazolidinone with aldehydes. Under the nitrogen atmosphere, samarium powder (Nippon Yttrium Co., Ltd., 99.9%) (350 mg, 2.2 mmol) was placed in a 50-mL Schlenk tube equipped with a magnetic stirring bar. A dry THF (20 mL) solution of diiodomethane (540 mg, 2.0 mmol) was added using a syringe through a septum. The mixture was stirred for 2 h at room temperature, and samarium(II) iodide solution was obtained as a deep green solution. The Schlenk tube was cooled in a dry ice−methanol bath, and a mixture of isobutyraldehyde (80 mg, 1.0 mmol) and **1** (250 mg, 1.0 mmol) in dry THF (2 mL) was slowly dropwise injected over a period of 5 min. The resulting solution was stirred at −78 °C for 0.5 h, during which time the deep green color of the solution faded. The solution was hydrolyzed with 25 mL of 0.1 mol/L hydrochloric acid, and the aqueous phase was extracted with three 20 mL portions of diethyl ether. The organic phase was washed with aqueous sodium thiosulfate to remove liberated iodine and brine and then dried over magnesium sulfate. The solvent was removed under reduced pressure, and the yellow residue was subjected to preparative TLC on silica gel (hexane/ethyl acetate = 2:1 as eluent) to afford a mixture of the diastereomers of 4*S*-3-[3-hydroxy-4-methylpentanoyl]-4-(1-methylethyl)-2-oxazolidinone (**7a**) as a colorless liquid (223 mg, 0.92 mmol, 92% yield). The diastereomeric excess of 83% the product was determined by GC/MS analysis after trifluoroacetylation with trifluoroacetic anhydride. The absolute configuration of the 3-alcoholic carbon was determined after transesterification leading to the $\beta$-hydroxy ester (vide infra): $[\alpha]^{20}_D = +95.07$ ($c = 0.588$, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.82 (d, 3H, $J = 7.0$ Hz), 0.86 (d, 3H, $J = 7.0$ Hz), 0.89 (d, 3H, $J = 6.9$ Hz), 0.91 (d, 3H, $J = 6.9$ Hz), 1.6−1.7 (m, 1H), 2.2−2.4 (m, 1H), 2.90 (br s, 1H), 2.94 (dd, 1H, $J = 10.0$, 17.1 Hz), 3.09 (dd, 1H, $J = 2.5$, 16.8 Hz), 3.82 (m, 1H), 4.23 (dd, 1H, $J = 3.0$, 9.0 Hz), 4.28 (dd, 1H, $J = 8.1$, 9.0 Hz), 4.45 (ddd, 1H, $J = 3.0$, 3.9, 8.1 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.4, 17.6, 28.2, 39.6, 46.1, 58.1, 63.2, 68.9, 153.9, 172.9; IR ($CCl_4$) 3567 ($\nu_{OH}$), 1791, 1691 ($\nu_{C=O}$) cm$^{-1}$. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.47; H, 8.68; N, 5.59.

(20) Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, 56, 2489.

(21) Addition of more than 4 equiv of hexamethylphosphoric amide to samarium(II) iodide remarkably decreased the diastereoselectivity (59% de) in **7a**, suggesting the chelation control should be involved in the high diastereoselectivity.

**Transesterification of the β-Hydroxy Carboximide with Sodium Ethoxide.** In a two-neck round-bottom flask containing a magnetic stirring bar were charged a diastereomeric mixture of **7a** (120 mg, 0.50 mmol, 83% de) and anhydrous ethanol (5 mL). The flask was then cooled in an ice bath, and an ethanolic (1 mL) solution of sodium ethoxide (70 mg, 1.0 mmol) was added. The resulting mixture was stirred at 0 °C, and the reaction was monitored by TLC. After 20 min, the reaction mixture was quenched with aqueous ammonium chloride and extracted with three 15 mL portions of diethyl ether. The combined extracts were dried over magnesium sulfate, and the solvent was removed on a rotary evaporator to give a pale yellow residue. The residue was subjected to preparative TLC (silica gel, hexane/ethyl acetate = 4:1): $R_f = 0.3$, ethyl 3*R*-hydroxy-4-methylpentanoate (**8a**), 72 mg, 0.45 mmol, 90% yield; $R_f = 0.1$, 4*S*-(1-methylethyl)-2-oxazolidinone, 116 mg, 0.90 mmol, 90% recovered): colorless liquid; $[\alpha]^{20}_D = +32.34$ ($c = 0.708$, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.92 (d, 3H, $J = 6.9$ Hz), 0.96 (d, 3H, $J = 6.7$ Hz), 1.28 (t, 3H, $J = 7.1$ Hz), 1.73 (oct, 1H, $J = 6.6$ Hz), 2.42 (dd, 1H, $J = 9.5$, 16.4 Hz), 2.50 (dd, 1H, $J = 2.7$, 16.3 Hz), 3.78−3.81 (ddd, 1H, $J = 2.9$, 6.4, 9.5 Hz), 4.18 (q, 2H, $J = 7.0$ Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.1, 17.7, 18.3, 33.1, 38.4, 60.6, 72.7, 173.0. GC analysis of trifluoroacetylated ethyl 3*R*-hydroxy-4-methyl pentanoate using chiral capillary column (Astec, Chiraldex G-TA, 30 m) revealed that the ee value (83%) was consistent with the de value of the parent β-hydroxy carboximide.

**Hydrolysis of the β-Hydroxy SuperQuat with Lithium Hydroxide.** In a two-neck round-bottom flask containing a magnetic stirring bar were charged a diastereomeric mixture of **7m** (305 mg, 1.0 mmol, 49% de) and THF (15 mL). The flask was then cooled in an ice bath, and an aqueous (3 mL) solution of lithium hydroxide (50 mg, 2.0 mmol) was added. The resulting mixture was stirred at 0 °C, and the reaction was monitored by TLC. After 30 min, the reaction mixture was quenched with aqueous sodium bicarbonate and extracted with three 20 mL portions of diethyl ether: the SuperQuat was extracted into organic layer and sequential procedure, drying ($MgSO_4$), filtration, and evaporation of solvent, gave 149 mg (95%) of the crude SuperQuat. Aqueous layer was then acidified by concentrated hydrochloric acid and extracted with three 20 mL portions of diethyl ether. The combined extracts were dried over magnesium sulfate, and the solvent was removed on a rotary evaporator to give a pale yellow liquid. 3*R*-hydroxy-4-methylpentanoic acid (**9m**), 141 mg, 0.85 mmol, 85% yield: $[\alpha]^{20}_D = +29.52$($c = 0.21$, $CHCl_3$); $^1$H NMR ($CDCl_3$,-400 MHz) $\delta$ 2.77 (dd, 1H, $J = 3.8$, 16.6 Hz), 2.85 (dd, 1H, $J = 9.3$, 16.6 Hz), 5.17 (dd, 1H, $J = 3.6$, 9.3 Hz), 7.5−7.7 (m, 5H).

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**Supporting Information Available:** Spectral and analytical data of compounds **2**−**5** and **7b**−**q** and copies of $^1$H and $^{13}$C NMR spectra of **1**−**5** and **7a**−**q**. This material is available free of charge via the Internet at http://pubs.acs.org.

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