Samarium(II) Iodide Mediated Intermolecular Coupling Reactions of *N,N*-Dibenzyl-α-haloamides with Carbonyl Compounds

Yutaka Aoyagi, Rie Asakura, Nobuko Kondoh, Rieko Yamamoto, Takeshi Kuromatsu, Ai Shimura, Akihiro Ohta*
School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan
Fax +81(426)752605
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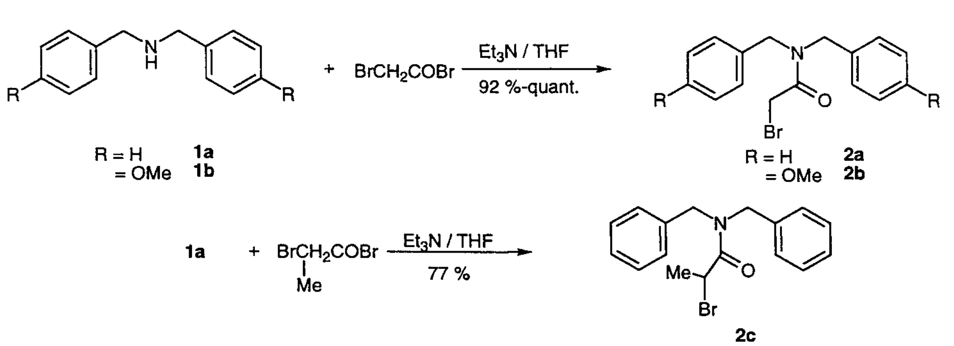
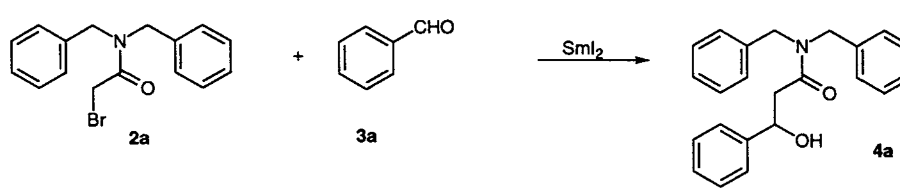
Samarium(II) iodide mediated coupling reactions of α-haloamides with carbonyl compounds are found to give *N,N*-dibenzyl-β-hydroxyamides (**4a–i**, **5a–i**, and **6a**) in good yields under mild reaction conditions. The transformation of **4a** and **5a** to *N,N*-dibenzyl-3-phenylpropanamide (**7**) and β-hydroxycarboxylic acid (**8**), respectively, are described.

Many publications during the past 15 years have shown the versatility of samarium(II) iodide (SmI_2) as a reagent in organic synthesis.[1,2] Since Kagan and co-workers reported the SmI_2 mediated intermolecular Reformatsky-type reactions between ethyl α-bromoacetate and cyclohexanone,[3] many SmI_2 mediated Reformatsky-type reactions have been described.[4–6] However, most of them are restricted to entropically favored intramolecular reactions, but with some exceptions. For example, Zhang et al. reported the SmI_2 mediated intermolecular coupling reactions between α-halo ketones and aldehydes with an electron-withdrawing group to give α,β-enones.[7] Recently, we reported the SmI_2 mediated intermolecular aldol-type reactions of phenacyl bromides with carbonyl compounds as a route to β-hydroxy ketones.[8] However, little is known about the SmI_2 mediated intermolecular coupling reactions of α-haloamides with carbonyl compounds. In this paper, we report the SmI_2 mediated intermolecular coupling reactions of *N,N*-dibenzyl-α-haloamide **2a** with several kinds of carbonyl compounds giving *N,N*-dibenzyl-β-hydroxyamides. In addition, the transformation of *N,N*-dibenzyl-β-hydroxyacetamide (**4a**) to *N,N*-dibenzyl-3-phenylpropanamide (**7**) using hydrogenolysis conditions is described. As well as this, it is shown that the treatment of *N,N*-bis(4-methoxybenzyl)-β-hydroxyacetamides **5** with ceric(IV) ammonium nitrate (CAN) in a mixture of acetonitrile and water (2:1) gives β-hydroxycarboxylic acids **8**, which are biologically active compounds.[9] *N,N*-Dibenzyl-α-bromoacetamides (**2a–c**) were initially prepared *via* the reactions of *N,N*-dibenzylamines (**1a–b**) with α-bromocarboxylic acid bromides (Scheme 1).



Scheme 1

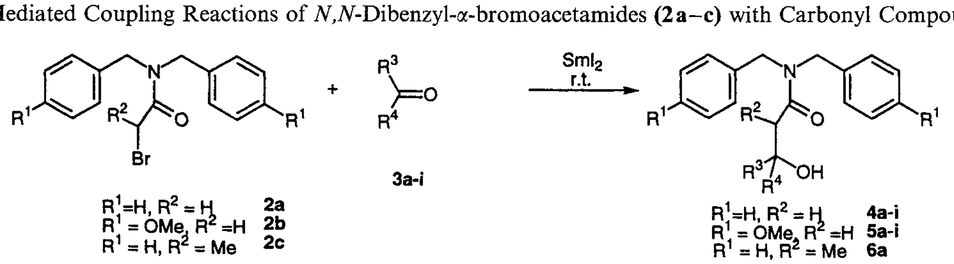
Table 1. SmI_2 Mediated Coupling Reactions of *N,N*-Dibenzyl-α-bromoacetamide (**2a**) with Benzaldehyde (**3a**)



Entry	Reaction Conditions			Yield (%) of **4a**
	Method[a]	Additive	Reaction Temperature (°C)	
1	A1	none	0	61
2	A2	none	0	46
3	A1	Et_2AlCl[b]	0	64
4	A1	HMPA[c]	−78	trace
5	A1	none	−78	many products
6	A1	none	r.t.	88

[a] Method A1: SmI_2 in THF was added to a THF solution of substrate.
Method A2: A THF solution of substrate was added to a solution of SmI_2 in THF.
[b] Ratio Et_2AlCl: aldehyde = 2:1.
[c] 10% (V/V) HMPA in THF was added.

Table 2. SmI_2 Mediated Coupling Reactions of *N,N*-Dibenzyl-α-bromoacetamides (**2a–c**) with Carbonyl Compounds (**3a–i**)



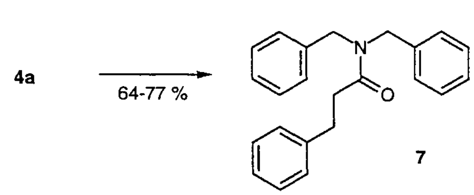
Entry	α-Haloamide	Carbonyl Compound	Product	Yield (%)
1	**2a**	Benzaldehyde (**3a**)	**4a**	88
2	**2b**	Benzaldehyde (**3a**)	**5a**	78
3	**2a**	Benzaldehyde (**3a**)	**6a**	79 (35:65)[a,b]
4	**2c**	*o*-Tolualdehyde (**3b**)	**5b**	67
5	**2a**	Octanal (**3c**)	**4c**	78
6	**2b**	Octanal (**3c**)	**5c**	79
7	**2a**	Acetophenone (**3d**)	**4d**	80
8	**2b**	Acetophenone (**3d**)	**5d**	74
9	**2a**	Benzophenone (**3e**)	**4e**	78
10	**2b**	Benzophenone (**3e**)	**5e**	67
11	**2a**	Cyclohexanone (**3f**)	**4f**	77
12	**2b**	Cyclohexanone (**3f**)	**5f**	76
13	**2a**	*β*-Tetralone (**3g**)	**4g**	87
14	**2b**	*β*-Tetralone (**3g**)	**5g**	84
15	**2a**	Cyclopenten-1-one (**3h**)	**4h**	78
16	**2b**	Cyclopenten-1-one (**3h**)	**5h**	61
17	**2a**	2-Methylpentan-2-one (**3i**)	**4i**	67
18	**2b**	2-Methylpentan-2-one (**3i**)	**5i**	69

[a] The ratio of the diastereomers was determined by ^1H NMR.
[b] The relative configuration of the diastereomers could not be determined.

Next, to determine the optimum conditions, the reaction of *N,N*-dibenzyl-α-bromoacetamide (**2a**) with benzaldehyde (**3a**) was examined under a variety of conditions. Table 1 summarizes the results of all the experiments that we conducted. The addition of hexamethylphosphoramide (HMPA) and diethylaluminum chloride (Et_2AlCl)[8] was ineffective (Entries 3 and 4 in Table 1). The reaction temperature significantly affected the yields of **4a** (Entries 1, 5, and 6 in Table 1). When the reaction was carried out at room temperature, the best result was obtained.

Under the conditions of Entry 6 in Table 1, the corresponding *N,N*-dibenzyl-*β*-hydroxyacetamide (**4a**) was obtained in satisfactory yield. We then allowed *N,N*-dibenzyl-α-bromoacetamide (**2a**), *N,N*-bis(4-methoxybenzyl)-α-bromoacetamide (**2b**), and *N,N*-dibenzyl-α-bromopropionamide (**2c**) to react with several kinds of aldehydes (**3a–i**). Their reaction results are shown in Table 2.

N,N-Dibenzyl-*β*-hydroxyamides **4–6** are obtained in moderate to good yields and the scope of the reaction is broad (Entries 1–18 in Table 2). With a sterically hindered aldehyde **3b** and ketone **3i**, the yields are slightly reduced (Entries 4, 17, and 18 in Table 2). The reactions of α-haloamides (**2a** and **2b**) with *α,β*-unsaturated ketone **3h** are regioselective and yield only the 1,2-addition products (**4h** and **5h**) (Entries 15 and 16 in Table 2). With the enolizable ketone **3g**, the corresponding *β*-hydroxyamides (**4g** and **5g**) were produced in moderate yields (Entries 13 and 14 in Table 2). The diastereoselectivity was not observed in Entry 3 in Table 2. The conversion of the obtained *N,N*-dibenzyl-*β*-hydroxyacetamide (**4a**) was then examined (Scheme 2). The *N*-debenzylation of **4a** was unsuccessful under the conditions of Entries 1 and 2 in Scheme 2. In both runs, dehydroxylation proceeded to give compound **7** in 64–77% yields.

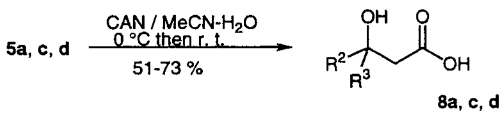


Entry	Condition	Yield (%)
1	H_2 / 10%Pd-C / MeOH	64
2	Pd(black) / HCOOH / MeOH	77

Scheme 2

Finally, the debenzylation of *N,N*-bis(4-methoxybenzyl)-*β*-hydroxyacetamides (**5a**, **c**, and **d**) were attempted (Table 3). The treatment of **5a**, **c**, and **d** with CAN in a mixture of acetonitrile and water (2:1) gave the corresponding *β*-hydroxycarboxylic acid **8a**,[10] **c**[9,11] and **d**,[10] respectively. Compound **8c** is myrmicacine, a pheromone secreted by myrmicine ants, having an antiseptic effect on bacteria, yeast and mold.[9]

Table 3. Debenzylation of *N,N*-Bis(4-methoxybenzyl)-β-hydroxyamides (**5**) with CAN



Entry	Substrate	Product	Yield (%)
1	**5a**	**8a**[10]	51
2	**5c**	**8c**[9, 11]	68
3	**5d**	**8d**[10]	73

In conclusion, the SmI_2 mediated coupling reactions of *N,N*-dibenzyl-α-haloamides with several kinds of carbonyl compounds proceeded to give *N,N*-dibenzyl-β-hydroxyamides in good yields under mild reaction conditions. *N,N*-Dibenzyl-β-hydroxyamide (**4a**) was converted to the dehydroxylated compound (**7**) under the conditions of hydrogenolysis. Also, *N,N*-bis(4-methoxybenzyl)-β-hydroxyamides (**5a**, **c**, and **d**) were debenzylated with CAN in a mixture of acetonitrile and water (2:1) to give the corresponding β-hydroxycarboxylic acids (**8a**, **c**, and **d**).

Table 4. Physical and Spectral Data of Compounds **2a–c**, **4a–i**, **5a–i**, **6a**, and **7** Prepared.[a,b]

Product[a]	Yield[c] (%)	Crystal (mp °C, solvent) or oil	IR ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	Ms (70 eV) m/z
2a	92	colorless viscous oil	1650 (C=O)	7.41–7.16 (m, 10 H), 4.63 (s, 2 H), 4.53 (s, 2 H), 3.92 (s, 2 H)	318 ($M^+ + 1$)[d] 320 ($M^+ + 3$)
2b	quant.	colorless viscous oil	1650 (C=O)	7.17–7.08 (m, 4 H), 6.92–6.85 (m, 4 H), 4.53 (s, 2 H), 4.44 (s, 2 H), 3.93 (s, 2 H), 3.83 (s, 3 H), 3.81 (s, 3 H)	377 (M^+) 379 ($M^+ + 2$)
2c	77	colorless prisms (56–57)	1650 (C=O)	7.41–7.22 (m, 8 H), 7.14 (d, 2 H, J = 6.7), 5.29 (d, 1 H, J = 14.8), 4.78 (d, 1 H, J = 17.1), 4.52 (q, 1 H, J = 6.6), 4.34 (d, 1 H, J = 17.5), 4.02 (d, 1 H, J = 14.9)	332 (M^+) 334 ($M^+ + 2$)
4a	88	colorless prisms (103–104, *i*-Pr_2O)	3500 (OH), 1620 (C=O)	7.38–7.09 (m, 15 H), 5.22 (m, 1 H), 4.78 (d, 1 H, J = 3.0), 4.73 (d, 1 H, J = 14.8), 4.51 (d, 1 H, J = 14.8), 4.43 (d, 1 H, J = 16.5), 4.35 (d, 1 H, J = 17.2), 2.82 (dd, 1 H, J = 18.3 and 7.0), 2.76 (dd, 1 H, J = 18.8 and 1.8)	345 (M^+) 327 ($M^+ - H_2O$)
4c	78	colorless viscous oil	3440 (OH), 1635 (C=O)	7.41–7.13 (m, 10 H), 4.68 (d, 1 H, J = 14.6), 4.55 (d, 1 H, J = 14.8), 4.47 (d, 1 H, J = 17.4), 4.40 (d, 1 H, J = 16.8), 4.27 (d, 1 H, J = 2.6), 4.08 (m, 1 H), 2.59 (dd, 1 H, J = 16.4 and 2.5), 2.44 (dd, 1 H, J = 16.4 and 9.4), 1.57–1.18 (m, 12 H), 0.87 (t, 3 H, J = 7.0)	367 (M^+)
4d	80	colorless needles (113–114, *i*-Pr_2O)	3400 (OH), 1610 (C=O)	7.45–7.05 (m, 13 H), 6.86 (m, 2 H), 6.30 (s, 1 H), 4.69 (d, 1 H, J = 14.9), 4.46 (d, 1 H, J = 17.0), 4.32 (d, 1 H, J = 14.6), 4.27 (d, 1 H, J = 16.7), 3.15 (d, 1 H, J = 15.6), 2.73 (d, 1 H J = 15.7), 1.54 (s, 3 H)	341 ($M^+ - H_2O$)
4e	78	colorless needles (102–103, *i*-Pr_2O)	3340 (OH), 1625 (C=O)	7.42–7.12 (m, 18 H), 6.93–6.90 (m, 2 H), 6.85 (s, 1 H), 4.56 (s, 2 H), 4.45 (s, 2 H), 3.34 (s, 2 H)	421 (M^+) 403 ($M^+ - H_2O$)
4f	77	colorless viscous oil	3420 (OH), 1630 (C=O)	7.41–7.13 (m, 10 H), 5.23 (s, 1 H), 4.63 (s, 2 H), 4.46 (s, 2 H), 2.51 (s, 2 H), 1.78–1.17 (m, 10 H)	337 (M^+) 319 ($M^+ - H_2O$)
4g	87	colorless viscous oil	3425 (OH), 1630 (C=O)	7.36–7.22 (m, 9 H), 7.11–7.02 (m, 6 H), 4.64 (s, 2 H), 4.39 (d, 1 H, J = 16.8), 4.30 (d, 1 H, J = 17.1), 3.13–3.01 (m, 1 H), 3.04 (d, 1 H, J = 17.5), 2.82 (d, 1 H, J = 16.2), 2.72–2.55 (m, 3 H), 2.05 (m, 1 H), 1.82 (m, 1 H)	386 ($M^+ + 1$) 367 ($M^+ - H_2O$)
4h	78	colorless prisms (83–84, *i*-Pr_2O)	3380 (OH), 1620 (C=O)	7.40–7.21 (m, 8 H), 7.13 (d, 2 H, J = 8.0), 5.90–5.83 (m, 2 H), 5.40 (s, 1 H), 4.67 (d, 1 H, J = 14.8), 4.59 (d, 1 H, J = 14.8), 4.42 (s, 2 H), 2.73 (s, 2 H), 2.57–2.46 (m, 1 H), 2.26–2.04 (m, 2 H), 1.95–1.86 (m, 1 H)	321 (M^+) 303 ($M^+ - H_2O$)
4i	67	colorless viscous oil	3410 (OH), 1620 (C=O)	7.41–7.22 (m, 8 H), 7.16–7.14 (m, 2 H), 5.34 (br s, 1 H), 4.68 (d, 1 H, J = 14.7), 4.62 (d, 1 H, J = 14.6), 4.47 (s, 2 H), 2.51 (d, 1 H, J = 15.8), 2.45 (d, 1 H, J = 16.1), 1.93 (m, 1 H), 1.62–1.59 (m, 2 H), 0.88 (d, 3 H, J = 6.9), 0.87 (t, 3 H, J = 7.5), 0.83 (d, 3 H, J = 6.9)	339 (M^+) 321 ($M^+ - H_2O$)
5a	78	colorless prisms (94–95, *i*-Pr_2O)	3380 (OH), 1620 (C=O)	7.38–7.26 (m, 5 H), 7.13 (d, 2 H, J = 8.8), 7.00 (d, 2 H, J = 8.8), 6.87 (d, 2 H, J = 8.6), 6.86 (d, 2 H, J = 8.7), 5.21 (m, 1 H), 4.85 (d, 1 H, J = 3.0), 4.61 (d, 1 H, J = 14.6), 4.44 (d, 1 H, J = 14.5), 4.33 (d, 1 H, J = 17.1), 4.26 (d, 1 H, J = 17.1), 3.815 (s, 3 H), 3.810 (s, 3 H), 2.87 (dd, 1 H, J = 16.4 and 4.1), 2.76 (dd, 1 H, J = 16.5 and 8.0)	406 ($M^+ + 1$)[d] 388 ($M^+ - OH$)

Table 4. (continued)

Product[a]	Yield[c] (%)	Crystal (mp °C, solvent) or Oil	IR ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	Ms (70 eV) m/z
5b	67	colorless prisms (75–76, i-Pr_2O)	3420 (OH), 1615 (C=O)	7.55 (dd, 1 H, J = 7.4 and 1.4), 7.25–7.08 (m, 3 H), 7.17 (d, 2 H, J = 7.2), 7.01 (d, 2 H, J = 8.7), 6.874 (d, 2 H, J = 8.6), 6.867 (d, 2 H, J = 8.7), 5.41 (ddd, 1 H, J = 8.4, 3.0, and 3.0), 4.82 (d, 1 H, J = 2.6), 4.75 (d, 1 H, J = 14.6), 4.35 (d, 1 H, J = 14.4), 4.33 (d, 1 H, J = 16.8), 4.25 (d, 1 H, J = 16.8), 3.81 (s, 6 H), 2.74 (dd, 1 H, J = 16.2 and 3.3), 2.66 (dd, 1 H, J = 16.3 and 8.4), 2.22 (s, 3 H)	418 (M^+ + 1) 402 (M^+ – OH)
5c	79	colorless viscous oil	3450 (OH), 1615 (C=O)	7.14 (d, 2 H, J = 8.6), 7.06 (d, 2 H, J = 8.8), 6.90 (d, 2 H, J = 8.7), 6.85 (d, 2 H, J = 8.7), 4.57 (d, 1 H, J = 14.6), 4.47 (d, 1 H, J = 14.6), 4.34 (s, 2 H), 4.33 (br s, 1 H), 4.07 (m, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 2.58 (dd, 1 H, J = 16.3 and 2.4), 2.42 (dd, 1 H, J = 16.4 and 9.4), 1.61–1.21 (m, 12 H), 0.87 (t, 3 H, J = 6.9)	428 (M^+ + 1)[d] 409 (M^+ – H_2O)
5d	74	colorless viscous oil	3360 (OH), 1610 (C=O)	7.45–7.26 (m, 5 H), 6.97 (d, 2 H, J = 8.8), 6.88 (d, 2 H, J = 8.8), 6.80 (d, 2 H, J = 8.9), 6.75 (d, 2 H, J = 8.9), 6.35 (s, 1 H), 4.58 (d, 1 H, J = 14.6), 4.37 (d, 1 H, J = 16.8), 4.23 (d, 1 H, J = 15.1), 4.18 (d, 1 H, J = 17.0), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.14 (d, 1 H, J = 15.5), 2.71 (d, 1 H, J = 15.5), 1.54 (s, 3 H)	419 (M^+) 402 (M^+ – OH)
5e	67	colorless viscous oil	3400 (OH), 1640 (C=O)	7.40–7.38 (m, 4 H), 7.32–7.23 (m, 6 H), 7.03 (d, 2 H, J = 8.6), 6.91 (d, 2 H, J = 8.9), 6.85 (d, 2 H, J = 8.5), 6.76 (d, 2 H, J = 8.8), 4.45 (s, 2 H), 4.36 (s, 2 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.32 (s, 2 H)	463 (M^+ – H_2O) 481 (M^+)
5f	76	colorless viscous oil	3420 (OH), 1615 (C=O)	7.14 (d, 2 H, J = 8.7), 7.05 (d, 2 H, J = 8.7), 6.90 (d, 2 H, J = 8.7), 6.86 (d, 2 H, J = 8.7), 5.33 (br s, 1 H), 4.52 (s, 2 H), 4.36 (s, 2 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 2.49 (s, 2 H), 1.77–1.51 (m, 6 H), 1.42–1.17 (m, 4 H)	397 (M^+)
5g	84	colorless viscous oil	3400 (OH), 1615 (C=O)	7.17 (d, 2 H, J = 8.6), 7.12–7.01 (m, 4 H), 6.95 (d, 2 H, J = 8.7), 6.88 (d, 2 H, J = 8.7), 6.83 (d, 2 H, J = 8.6), 5.61 (s, 1 H), 4.58 (d, 1 H, J = 14.6), 4.52 (d, 1 H, J = 14.4), 4.30 (d, 1 H, J = 16.8), 4.21 (d, 1 H, J = 16.8), 3.82 (s, 3 H), 3.80 (s, 3 H), 3.80 (s, 3 H), 3.06 (m, 1 H), 3.03 (d, 1 H, J = 16.4), 2.82 (d, 1 H, J = 16.4), 2.70 (m, 1 H), 2.66 (d, 1 H, J = 16.0), 2.57 (d, 1 H, J = 16.0), 2.05 (m, 1 H), 1.80 (m, 1 H)	445 (M^+) 427 (M^+ – H_2O)
5h	61	colorless viscous oil	3410 (OH), 1615 (C=O)	7.16 (d, 2 H, J = 8.8), 7.05 (d, 2 H, J = 8.8), 6.90 (d, 2 H, J = 9.0), 6.87 (d, 2 H, J = 9.0), 5.91–5.83 (m, 2 H), 5.47 (s, 1 H), 4.57 (d, 1 H, J = 14.6), 4.50 (d, 1 H, J = 14.6), 4.34 (s, 2 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 2.72 (s, 2 H), 2.59–2.47 (m, 1 H), 2.28–2.17 (m, 1 H), 2.14–2.05 (m, 1 H), 1.95–1.87 (m, 1 H)	363 (M^+ – H_2O)
5i	69	colorless viscous oil	3400 (OH), 1615 (C=O)	7.16 (d, 2 H, J = 8.3) 7.06 (d, 2 H, J = 8.6), 6.90 (d, 2 H, J = 8.8), 6.86 (d, 2 H, J = 8.7), 5.41 (br s, 1 H), 4.55 (s, 2 H), 4.38 (s, 2 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 2.47 (s, 2 H), 1.93 (m, 1 H), 1.61–1.51 (m, 2 H), 0.88 (t, 3 H, J = 6.0), 0.87 (d, 3 H, J = 7.3), 0.84 (d, 3 H, J = 6.9).	400 (M^+ + 1) 382 (M^+ – OH)
6a	79	colorless prisms (147–149, i-Pr_2O)	3400 (OH), 1630 (C=O)	7.44–6.93 (m, 15 H), 5.05 (d, 1 H, J = 14.5), 4.82 (d, 1 H, J = 13.8), 4.61–4.26 (m, 3 H), 3.14 (m, 0.35 H), 2.89 (m, 0.65 H), 1.30 (d, 1.05 H, J = 7.1), 1.13 (d, 1.95 H, J = 7.0)	360 (M^+ + 1) 341 (M^+ – H_2O)
7	64–77	colorless prisms (105–106, i-Pr_2O)	1635 (C=O)	7.33–7.07 (m, 15 H), 4.63 (s, 2 H), 4.37 (s, 2 H), 3.06 (t, 2 H, J = 8.0), 2.72 (t, 2 H, J = 8.2)	329 (M^+), 238 (M^+ – $CH_2C_6H_5$)

[a] Satisfactory microanalysis obtained for **2b**, **4a**, **d**, **e**, **h**, **5a**, **b**, **6a** and **7**: C ± 0.43, H ± 0.18, N ± 0.26.
[b] Deviation in HRMS spectra for **2a**, **c**, **4c**, **f**, **g**, **i**, **5c**, **d**, **e**, **f**, **g**, **h** and **i**: ± 0.0027.
[c] Yield of pure, isolated product.
[d] Cl-MS.

Further studies dealing with the diastereoselective coupling reactions of chiral α-haloamides with carbonyl compounds are in progress.

Melting points were obtained using a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO A-100 spectrometer or a Shimadzu spectrometer. ^1H NMR spectra were recorded as a solution in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard on a Varian GEMINI 300 spectrometer. Mass spectra were determined on a Faisons VG Auto Spec instrument. Medium-pressure liquid column chromatography (MPLC) was conducted using a UVILOG 5III spectrometer as the UV detector (Oyo Bunko kiki Co., Ltd. Tokyo) and Kieselgel 60 (Merck AG, Darmstadt) as the packing material. Preparative TLC was conducted using a Merck TLC plate (Art. 1.05744). A 1.0 M solution of Et_2AlCl in hexane and 0.1 M solution of SmI_2 in THF were purchased from the Aldrich Chem. Co. THF was distilled from purple sodium benzophenone ketyl under Ar immediately prior to use. HMPA (Aldrich Chem. Co., Ltd.) was distilled from CaH_2 at reduced pressure under Ar. Dibenzylamine, α-bromopropionyl bromide, and α-bromoacetyl bromide were purchased from Tokyo Kasei Co., Ltd. Bis(*p*-methoxybenzyl)amine was prepared according to the reported manner.[12]

_N,N_-Dibenzyl-α-bromoamides (2a–c); General Procedure:
α-Bromocarboxylic acid bromide (5.5 mmol) was added dropwise to a THF (10 mL) solution of **1** (5 mmol) and Et_3N (0.76 mL, 5.5 mmol) at 0 °C under Ar. After the resulting mixture was stirred at 0 °C for 15 min, the mixture was poured into ice/H_2O (30 mL). The mixture was then extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (3 × 20 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give an oily residue, which was purified with MPLC (hexane/EtOAc 4:1) to give **2** as a colorless oil.

_N,N_-Dibenzyl-β-hydroxyamides (4a–i, 5a–i, and 6a); General Procedure:
A 0.1 M SmI_2 solution in THF (30 mL, 3 mmol) was added dropwise to an anhyd THF (10 mL) solution of **2** (1 mmol) and **3** (1 mmol) at r.t. The mixture was stirred at r.t. for 1 h. To the mixture, sat. NH_4Cl (30 mL) and Et_2O (20 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layer was successively washed with brine (30 mL), 8 % $Na_2S_2O_3$ (30 mL), and brine. The organic solvent was dried (Na_2SO_4) and evaporated under reduced pressure to give an oily residue, which was purified with MPLC (hexane/EtOAc 4:1 ~ 2:1) to give **3**.

_N,N_-Dibenzylpropanamide (7):
a) Entry 1 (H_2/10 % Pd–C)

A mixture of **4a** (0.088 g, 0.267 mmol), 10 % Pd on carbon (0.018 g), and MeOH (20 mL) was stirred at r.t. under H_2 for 12 h. After the catalyst was filtered off through a short of Celite with MeOH (50 mL), the solvent was evaporated under reduced pressure to give a crystalline residue, which was purified by preparative TLC (hexane/EtOAc 4:1) to give **7** as colorless crystals; yield: 0.056 g (64 %).

b) Entry 2 [HCOOH/Pd (black)]

A mixture of **4a** (0.060 g, 0.20 mmol), Pd (black) (0.060 g), and 4 % HCOOH in MeOH (15 mL) was stirred at r.t. for 12 h. The catalyst was then filtered off through a short pad of Celite 545 with MeOH (50 mL), and the solvent was evaporated under reduced pressure to give a crystalline residue, which was purified by preparative TLC (hexane/EtOAc 4:1) to give **7** as colorless crystals; yield: 0.050 g (77 %).

β-Hydroxycarboxylic acids (8a, c, and d); General Procedure:
A solution of CAN (1.89 g, 3.45 mmol) in H_2O (2.5 mL) was added dropwise to a solution of **5** (0.69 mmol) in MeCN (5 mL) at 0 °C under Ar. The mixture was stirred at 0 °C for 1 h and then at r.t. for 3 h. To the mixture, brine (10 mL) was added. The resulting solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were extracted with 10 % $NaHCO_3$ (3 × 20 mL). After the aqueous layer was acidified to pH 3 with conc. HCl, the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude β-hydroxycarboxylic acid **8**, which was purified by recrystallization or preparative TLC.

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