

HETEROCYCLES, Vol. 94, No. 7, 2017, pp. 1337 - 1350. © 2017 The Japan Institute of Heterocyclic Chemistry  
Received, 15th April, 2017, Accepted, 19th May, 2017, Published online, 29th May, 2017  
DOI: 10.3987/COM-17-13725

## CATALYTIC ENANTIOSELECTIVE DESYMMETRIZATION OF *meso*-AZIRIDINES WITH FLUOROMALONATES<sup>†</sup>

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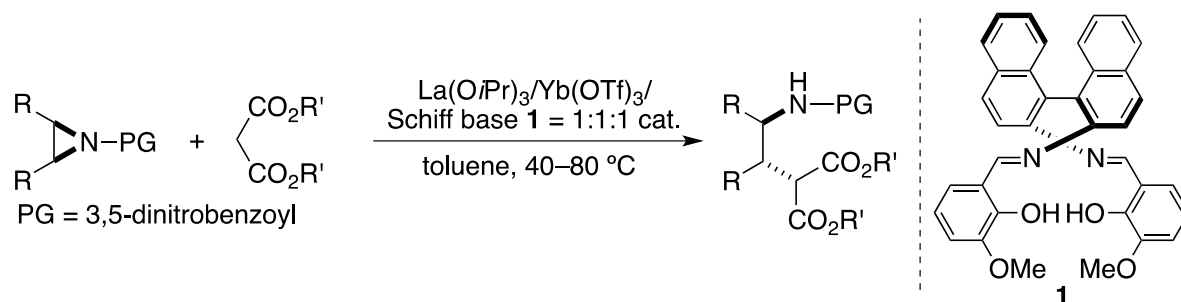
<sup>†</sup>Dedicated to Professor Masakatsu Shibasaki on the occasion of his 70th birthday

**Abstract** – Catalytic enantioselective desymmetrization of *meso*-aziridines with fluoromalonates is described. Optimization studies revealed that the appropriate combination of Brønsted basic metal and Lewis acidic metal is important for promoting the reaction using fluoromalonates. A heterodinuclear Gd(OiPr)<sub>3</sub>/Y(OTf)<sub>3</sub>/Schiff base = 1:1:1 was the best catalyst, and ring-opening adducts, synthetic precursors for  $\alpha$ -fluoro- $\gamma$ -amino acids, were obtained in 98%~17% yield and >99.5%~99% ee. Transformation of the ring-opening adduct into  $\alpha$ -fluoro- $\gamma$ -lactam was also demonstrated.

Fluorinated compounds play an important role in the pharmaceutical industry, because introducing fluorine atoms into biologically active compounds often improves the pharmacologic properties.<sup>1</sup> Most fluorinated pharmaceuticals have structurally simple fluoro- and trifluoromethyl-aromatic units, partly due to the ready availability of such units. On the other hand, the pharmaceutical industry now favors more three-dimensionally diverse cores rather than aromatic “flatland”.<sup>2</sup> Thus, a synthetic method that provides compounds bearing a fluorine atom attached to sp<sup>3</sup> carbons is in high demand. Various enantioselective synthetic methods for chiral fluorine building blocks were reported in the past decade.<sup>3</sup> In addition to asymmetric electrophilic and/or nucleophilic fluorination reactions,<sup>3</sup> the use of organofluoro nucleophiles in asymmetric reactions has been widely studied. Catalytic asymmetric alkylation, amination, aldol, Michael, and Mannich-type reactions were reported over the past decade.<sup>4,5</sup>

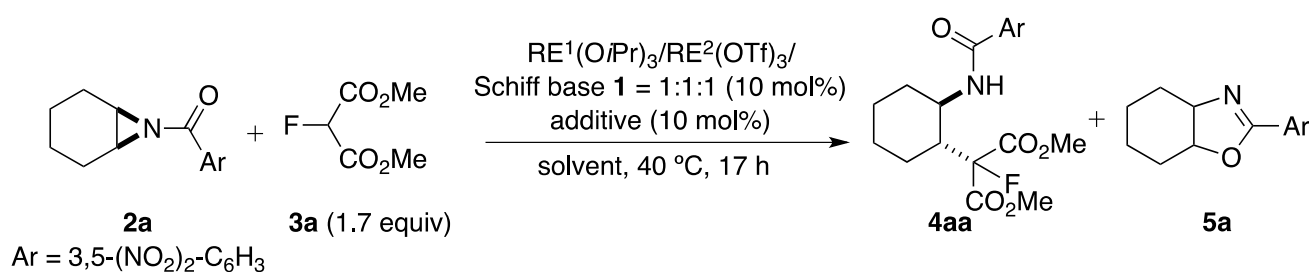
Among them, the use of commercially available fluoromalonates as nucleophiles is attractive for synthesizing diverse sets of chiral fluorine compounds as synthetic precursors of  $\alpha$ -fluoro carboxylic acids. Several groups have reported catalytic asymmetric Michael reactions<sup>6</sup> and Mannich-type reactions<sup>7</sup> with fluoromalonates that afford products in good to high enantioselectivity. Herein, we report our efforts to further broaden the reaction mode with fluoromalonates. We achieved a catalytic enantioselective desymmetrization of *meso*-aziridines with fluoromalonates for the first time, and ring-opening adducts bearing fluorine atom were obtained with high enantioselectivity.<sup>8</sup>

We, in collaboration with Shibasaki, previously developed catalytic asymmetric ring-opening reactions of aziridines with simple malonates under heterodinuclear rare earth metal-Schiff base catalysis (Scheme 1).<sup>9-12</sup> The combined use of La(OiPr)<sub>3</sub>, Yb(OTf)<sub>3</sub>, and Schiff base **1** was key for good reactivity and selectivity.<sup>11</sup> Thus, we applied the heterodinuclear catalysts to the reaction of *meso*-aziridine **2a** with fluoromalonate **3a**. Table 1 summarizes the optimization studies. The combination of a Brønsted basic rare earth metal alkoxide (RE<sup>1</sup>) and a Lewis acidic rare earth metal triflate (RE<sup>2</sup>) strongly affected the ratio of the desired ring-opening adduct **4aa** and undesired rearranged oxazoline **5a**. Using La(OTf)<sub>3</sub> together with La(OiPr)<sub>3</sub> resulted in **4aa** with high enantioselectivity (97% ee), but in poor yield (15%, entry 1). Selection of the Lewis acid was important for improving the yield of **4aa** (entries 2-6). Gd(OTf)<sub>3</sub> and Yb(OTf)<sub>3</sub> increased the yield of **4aa**, but also increased the yield of undesired **5a** at a similar ratio (entry 1 vs entries 3,4). Increasing the Lewis acidity using Y(OTf)<sub>3</sub><sup>13</sup> gave **4aa** in 45% yield, while the yield of **5a** was only 17% (entry 5). In contrast, Sc(OTf)<sub>3</sub>, the strongest Lewis acid among those screened,<sup>13</sup> predominantly promoted the undesired rearrangement into oxazoline, giving **5a** in 80% yield (entry 6). Changing the Brønsted basic rare earth metal alkoxides further improved the ratio of **4aa** and **5a** (entries 7-9), with Gd(OiPr)<sub>3</sub> in entry 8 producing the best results. On the other hand, the least Brønsted basic alkoxide Y(OiPr)<sub>3</sub> resulted in the predominant formation of undesired **5a**. These results suggested that the balance between Lewis acidity for activating the aziridine **2a** and Brønsted basicity for activating fluoromalonate **3a** is important for obtaining **4aa** over **5a**. We modified the reaction conditions to further improve the yield of **4aa** while suppressing the formation of **5a**. The addition of coordinating Et<sub>2</sub>O solvent and a catalytic amount of DMAP suppressed the undesired pathway, and **4aa** was obtained in 74% and 91% yield, respectively (entries 10 and 11). Finally, **4aa** was isolated in 96% yield and >99.5% ee in the presence of molecular sieves 3Å (entry 12). Under the optimized conditions, undesired **5a** was not detected. The absolute stereochemistry of **4aa** was unequivocally determined by single crystal X-ray analysis after transformation into **6** bearing heavy atoms (Figure 1). Reduction of the nitro groups in **4aa**, followed by coupling with 4-bromobenzoic acids, gave **6** in 60% yield (See, Supporting Information).



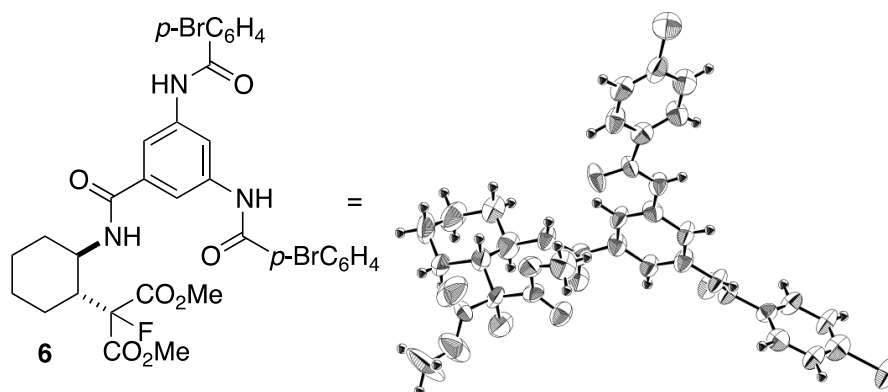
**Scheme 1.** Previous work on desymmetrization of aziridines with malonates

**Table 1.** Optimization of reaction conditions



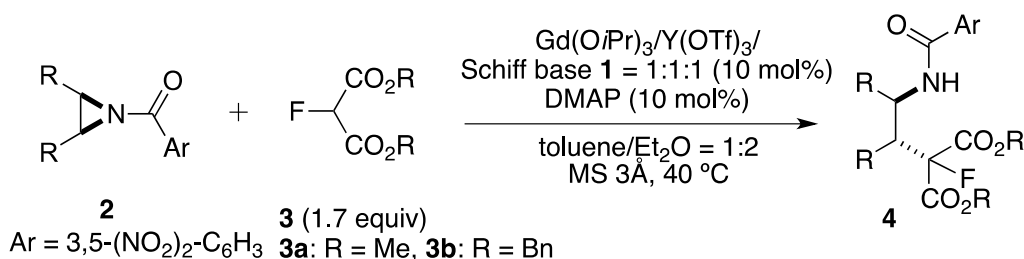
entry	RE <sup>1</sup> (OiPr) <sub>3</sub>	RE <sup>2</sup> (OTf) <sub>3</sub>	additive	solvent	% yield (4aa) <sup>a</sup>	% ee (4aa) <sup>b</sup>	% yield (5a) <sup>a</sup>
1	La(OiPr) <sub>3</sub>	La(OTf) <sub>3</sub>	none	toluene	15	97	13
2	La(OiPr) <sub>3</sub>	Sm(OTf) <sub>3</sub>	none	toluene	9	98	25
3	La(OiPr) <sub>3</sub>	Gd(OTf) <sub>3</sub>	none	toluene	22	99	21
4	La(OiPr) <sub>3</sub>	Yb(OTf) <sub>3</sub>	none	toluene	32	99.5	35
5	La(OiPr) <sub>3</sub>	Y(OTf) <sub>3</sub>	none	toluene	45	99	17
6	La(OiPr) <sub>3</sub>	Sc(OTf) <sub>3</sub>	none	toluene	N.D. <sup>c</sup>	–	80
7	Sm(OiPr) <sub>3</sub>	Y(OTf) <sub>3</sub>	none	toluene	48	99	26
8	Gd(OiPr) <sub>3</sub>	Y(OTf) <sub>3</sub>	none	toluene	48	99.5	11
9	Y(OiPr) <sub>3</sub>	Y(OTf) <sub>3</sub>	none	toluene	N.D. <sup>c</sup>	–	79
10	Gd(OiPr) <sub>3</sub>	Y(OTf) <sub>3</sub>	none	toluene/Et <sub>2</sub> O	74	>99.5	6
11	Gd(OiPr) <sub>3</sub>	Y(OTf) <sub>3</sub>	DMAP	toluene/Et <sub>2</sub> O	91 <sup>d</sup>	>99.5	N.D. <sup>c</sup>
12	Gd(OiPr) <sub>3</sub>	Y(OTf) <sub>3</sub>	DMAP + MS 3Å	toluene/Et <sub>2</sub> O	96 <sup>d</sup>	>99.5	N.D. <sup>c</sup>

<sup>a</sup> Determined by <sup>1</sup>H NMR analysis of crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard unless otherwise noted. <sup>b</sup> Determined by chiral HPLC analysis. <sup>c</sup> Not detected. <sup>d</sup> Isolated yield of product **4aa** after purification by silica gel column chromatography.



**Figure 1.** ORTEP drawing of **6** derived from **4aa**

Under the optimized reaction conditions, we investigated the substrate scope and limitations (Table 2). The reaction proceeded without difficulty using benzyl fluoromalonate **3b**, and **4ab** was obtained in 98% yield and >99.5% ee after 20 h (entry 2). On the other hand, the scope of aziridine was unexpectedly limited, and the reactivity drastically changed even by subtle changes in the substituents. Aziridine **2b** derived from cyclopentene gave desired product **4ba** in 96% yield and >99.5% ee, but required a long reaction time (72 h, entry 3). While dimethyl-substituted aziridine **2c** also gave product **4ca** in good yield (84%, entry 4), sterically more hindered aziridine **2d** bearing propyl substituents resulted in moderate yield (49%, entry 5). With aziridine **2e**, the standard reaction conditions afforded even worse results. Thus, we re-screened the additive, and **4ea** was obtained in 40% yield by using Et<sub>3</sub>N instead of DMAP and 20 mol% of the catalyst (entry 6). Aziridine **2f** was also one of the less reactive substrates, and desired product **4fa** was obtained in only 17% yield (entry 7). All attempts to improve the yield of **4fa** by modifying the reaction conditions failed. In all of the entries shown in Table 2, the enantioselectivity of product **4** was high (99%~>99.5% ee), but the yield changed depending on the aziridine structure. Although the reason for the observed results is unclear, a small conformational difference in each aziridine may affect the reactivity. Because the nucleophilicity of enolates derived from fluoromalonates is much lower than that derived from malonates, the distance between the reaction site of the aziridine and the nucleophile in the transition state might be crucial for promoting the desired aziridine opening reaction. Further studies to expand the scope of aziridines by modifying catalysts are ongoing in our group.

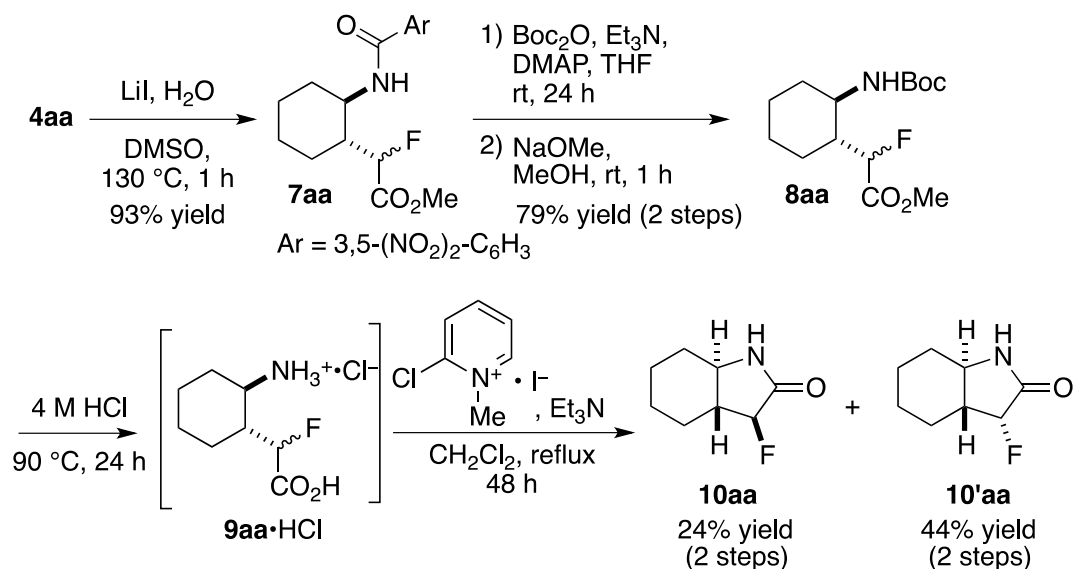
**Table 2.** Substrate scope and limitations of enantioselective desymmetrization of aziridines with fluoromalونات

entry	<b>2</b>	<b>3</b>	time (h)	<b>4</b>	% yield <sup>a</sup>	% ee <sup>b</sup>
1		<b>3a</b>	17	<b>4aa</b>	96	>99.5
2		<b>3b</b>	20	<b>4ab</b>	98	>99.5
3		<b>3a</b>	72	<b>4ba</b>	96	>99.5
4 <sup>c</sup>		<b>3a</b>	48	<b>4ca</b>	84	>99.5
5		<b>3a</b>	72	<b>4da</b>	49	99
6 <sup>d</sup>		<b>3a</b>	72	<b>4ea</b>	40	99
7		<b>3a</b>	72	<b>4fa</b>	17	>99.5

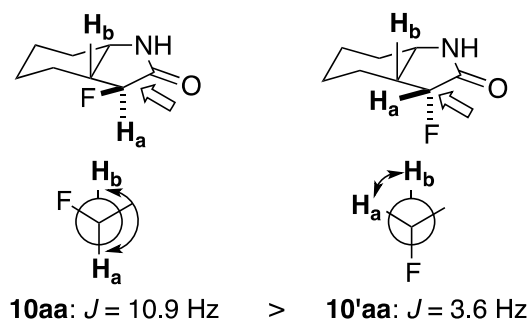
<sup>a</sup> Isolated yield after purification by column chromatography. <sup>b</sup> Determined by chiral HPLC analysis. <sup>c</sup> 1.1 equiv of **3a** was used. <sup>d</sup> The reaction was run using Et<sub>3</sub>N (20 mol%) instead of DMAP and 20 mol% of catalyst.

To demonstrate the synthetic utility of the ring-opening adduct, we transformed **4aa** into  $\alpha$ -fluoro- $\gamma$ -lactams **10** (Scheme 2). Decarboxylation of **4aa** proceeded smoothly with LiI/H<sub>2</sub>O in DMSO at 130 °C to give **7aa** in 93% yield as a 1:1 inseparable diastereomixture. The 3,5-dinitrobenzoyl group, which was required for asymmetric reaction,<sup>14</sup> was then exchanged with a Boc group in a two-step process. Introduction of the Boc group followed by treatment with NaOMe at ambient temperature gave **8aa** in 79% yield (2 steps; dr 1:2). Deprotection of **8aa** under acidic conditions proceeded to give  $\alpha$ -fluoro- $\gamma$ -amino acids **9aa**, which were then transformed into *trans*-fused bicyclic  $\gamma$ -lactams **10aa** (24%) and **10'aa** (44%) using 2-chloro-1-methylpyridinium iodide.<sup>15</sup>  $\gamma$ -Lactams **10aa** and **10'aa** were separable by silica gel column chromatography. The relative stereochemistry was assigned by <sup>1</sup>H NMR analysis. As

shown in Figure 2, the coupling constant between  $H_a$  and  $H_b$  in **10aa** was 10.9 Hz, while that in **10'aa** was only 3.6 Hz. The value matched the expected dihedral angle for each compound.



**Scheme 2.** Transformation of ring-opening product into  $\alpha$ -fluoro- $\gamma$ -lactams



**Figure 2.** Assignment of relative stereochemistry based on  $^1\text{H}$  NMR analysis

In summary, we achieved a highly enantioselective aziridine ring-opening reaction under heterodinuclear rare earth metal Schiff base catalysis. Although the aziridine scope was limited, the products were obtained in  $>99.5\%$ – $99\%$  ee and should be useful for synthesizing chiral  $\alpha$ -fluoro- $\gamma$ -amino acid derivatives.

## EXPERIMENTAL

**General.** Melting points were determined on a Büchi 535 digital melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer and absorbance bands are reported in  $\text{cm}^{-1}$ .  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on JEOL JNM-ECX400P spectrometer, JEOL JNM-ECS400 spectrometer, or JEOL JNM-ECA500 spectrometer. Optical rotations were measured on a

JASCO P-1030 digital polarimeter (at 589 nm). ESI-MS spectra were obtained on JEOL JMS-T100LC AccuTOF. HPLC was performed using JASCO PU-2080 pump, MD-4017 PDA detector with DAICEL CHIRALPAK IB or IC. Single crystal X-ray analysis was performed on a Rigaku R-AXIS RAPID/S imaging plate area detector with graphite-monochromated Cu-K $\alpha$  radiation. All non-aqueous reactions were carried out in a flame-dried glassware under an argon atmosphere unless otherwise noted. Dehydrated stabilizer-free diethyl ether, THF, and toluene were purchased from Kanto Chemical Co., Inc and purified by a solvent dispensing system supplied by Glass Contour (Nikko Hansen & Co., Ltd.).

**Preparation of Gd(O-*i*Pr)<sub>3</sub>/Y(OTf)<sub>3</sub>/Schiff base 1 = 1:1:1 Complex and General Procedure for Catalytic Asymmetric Ring-Opening of *meso*-Aziridines with 2-Fluoromalonate:** A test tube charged with MS 3Å (40.0 mg, 200 mg/mmol) was flame-dried under reduced pressure using a heat gun. After cooling to room temperature, argon was re-filled, Schiff base 1 (11.1 mg, 0.02 mmol), THF (0.2 mL) and Gd(O*i*Pr)<sub>3</sub> (0.2 M THF solution, 0.1 mL, 0.02 mmol) were added. The mixture was stirred at room temperature for 30 min to afford yellow suspension. THF was, then, removed under reduced pressure. To the test tube were added Y(OTf)<sub>3</sub> (10.7 mg, 0.02 mmol) and THF (0.20 mL), and the mixture was stirred at room temperature for 30 min to afford the Gd(O*i*Pr)<sub>3</sub>/Y(OTf)<sub>3</sub>/Schiff base = 1:1:1 catalyst in THF. Then, DMAP (2.4 mg, 0.02 mmol) was added, and THF was removed under reduced pressure. After drying the residue under reduced pressure for 1 h at room temperature, toluene (0.2 mL) and Et<sub>2</sub>O (0.4 mL) were added. To the resulting red suspension were added 2-fluoromalonate 3 (0.35 mmol, 1.7 equiv) and *meso*-aziridine 2 (0.20 mmol, 1.0 equiv), and the mixture was stirred for 17-72 h at 40 °C. After the mixture was cooled to room temperature and diluted with AcOEt, saturated EDTA•2Na *aq.* was added. The organic layer was separated, and the aqueous layer was extracted with AcOEt and the organic layers were washed with brine. The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation, the obtained crude mixture was purified by silica gel column chromatography (AcOEt/hexane/CH<sub>2</sub>Cl<sub>2</sub>) to give a corresponding product.

**Dimethyl 2-((1*R*,2*R*)-2-(3,5-dinitrobenzamido)cyclohexyl)-2-fluoromalonate (4aa):** colorless solid; mp 184.0-185.0 °C; IR (KBr)  $\nu$  3263, 3103, 2948, 1762, 1742, 1649, 1542, 1342, 1296 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.29-1.59 (m, 4H), 1.67-1.75 (m, 1H), 1.77-1.91 (m, 2H), 2.16-2.25 (m, 1H), 2.63-2.78 (m, 1H), 3.70 (s, 3H), 3.88 (s, 3H), 4.11-4.22 (m, 1H), 6.62 (d, *J* = 8.6 Hz, 1H), 8.95 (d, *J* = 2.0 Hz, 2H), 9.17 (t, *J* = 2.0 Hz, 1H); <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>, 100 MHz)  $\delta$  25.8 (d, *J*<sub>C-F</sub> = 21.3 Hz), 27.2 (d, *J*<sub>C-F</sub> = 2.3 Hz), 34.1, 47.0 (d, *J*<sub>C-F</sub> = 20.5 Hz), 49.2 (d, *J*<sub>C-F</sub> = 3.8 Hz), 53.5, 53.6, 96.8 (d, *J*<sub>C-F</sub> = 206 Hz), 121.7, 128.0, 138.5, 149.6, 162.1, 166.8 (d, *J*<sub>C-F</sub> = 25.8 Hz), 167.4 (d, *J*<sub>C-F</sub> = 26.6 Hz); HRMS (ESI): *m/z* calculated for C<sub>18</sub>H<sub>20</sub>O<sub>9</sub>N<sub>3</sub>FN<sup>+</sup> [M+Na]<sup>+</sup>: 464.1076, found: 464.1076 HPLC (chiral column: DAICEL

CHIRALPAK IC; solvent: hexane/2-propanol = 2/1; flow rate: 1.0 mL/min; detection: at 254 nm):  $t_R$  = 16.1 min (major) and 25.9 min (minor);  $[\alpha]_D^{25.9}$   $-38.2$  ( $c$  1.02, acetone).

**Dibenzyl 2-((1*R*,2*R*)-2-(3,5-dinitrobenzamido)cyclohexyl)-2-fluoromalonate (4ab):** colorless solid; mp 122.8-123.1 °C; IR (KBr)  $\nu$  3268, 2943, 1764, 1742, 1651, 1540, 1343, 1281, 1158, 701  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.15-1.53 (m, 4H), 1.55-1.84 (m, 3H), 2.11-2.22 (m, 1H), 2.61-2.79 (m, 1H), 4.07-4.22 (m, 1H), 5.04 (d,  $J$  = 9.1 Hz, 1H), 5.16-5.30 (m, 3H), 6.72 (d,  $J$  = 9.1 Hz, 1H), 7.02-7.13 (m, 5H), 7.23-7.36 (m, 5H), 8.72 (d,  $J$  = 2.0 Hz, 2H), 9.00 (t,  $J$  = 2.0 Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  24.6, 25.1, 26.4 (d,  $J_{\text{C-F}}$  = 3.6 Hz), 33.8, 45.4 (d,  $J_{\text{C-F}}$  = 20.4 Hz), 49.8 (d,  $J_{\text{C-F}}$  = 3.6 Hz), 67.8, 68.4, 96.0 (d,  $J_{\text{C-F}}$  = 206 Hz), 120.7, 126.9, 128.2, 128.3, 128.4, 128.6, 128.7, 134.1, 137.4, 148.3, 160.9, 165.7 (d,  $J_{\text{C-F}}$  = 26.4 Hz), 166.9 (d,  $J_{\text{C-F}}$  = 25.2 Hz); HRMS (ESI):  $m/z$  calculated for  $\text{C}_{30}\text{H}_{28}\text{O}_9\text{N}_3\text{FNa}^+$   $[\text{M}+\text{Na}]^+$ : 616.1702, found: 616.1704. HPLC (chiral column: DAICEL CHIRALPAK IC; solvent: hexane/2-propanol = 2/1; flow rate: 1.0 mL/min; detection: at 254 nm):  $t_R$  = 13.6 min (major) and 29.7 min (minor);  $[\alpha]_D^{26.0}$   $-1.8$  ( $c$  1.01, acetone).

**Dimethyl 2-((1*R*,2*R*)-2-(3,5-dinitrobenzamido)cyclopentyl)-2-fluoromalonate (4ba):** colorless solid; mp 139.2-139.8 °C; IR (KBr)  $\nu$  3347, 3083, 1761, 1742, 1647, 1542, 1343, 1248, 729  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.60-1.89 (m, 4H), 1.89-2.02 (m, 1H), 2.22-2.37 (m, 1H), 2.98-3.18 (m, 1H), 3.77 (s, 3H), 3.87 (s, 3H), 4.37-4.52 (m, 1H), 7.16 (d,  $J$  = 7.2 Hz, 1H), 8.98 (d,  $J$  = 2.0 Hz, 2H), 9.14 (t,  $J$  = 2.0 Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  22.7, 25.7 (d,  $J_{\text{C-F}}$  = 2.9 Hz), 33.6, 48.8 (d,  $J_{\text{C-F}}$  = 21.0 Hz), 51.8 (d,  $J_{\text{C-F}}$  = 2.8 Hz), 53.6, 53.7, 94.8 (d,  $J_{\text{C-F}}$  = 208 Hz), 121.0, 127.2, 137.8, 148.6, 162.3, 166.2 (d,  $J_{\text{C-F}}$  = 22.0 Hz), 166.5 (d,  $J_{\text{C-F}}$  = 22.0 Hz); HRMS (ESI):  $m/z$  calculated for  $\text{C}_{17}\text{H}_{18}\text{O}_9\text{N}_3\text{FNa}^+$   $[\text{M}+\text{Na}]^+$ : 450.0919, found: 450.0920; HPLC (chiral column: DAICEL CHIRALPAK IB; solvent: hexane/2-propanol = 2/1; flow rate: 1.0 mL/min; detection: at 254 nm):  $t_R$  = 10.9 min (major) and 25.5 min (minor);  $[\alpha]_D^{25.9}$   $-22.2$  ( $c$  0.99, acetone).

**Dimethyl 2-((2*R*,3*R*)-3-(3,5-dinitrobenzamido)butan-2-yl)-2-fluoromalonate (4ca):** colorless solid; mp 144.6-145.5 °C; IR (KBr)  $\nu$  3399, 1759, 1735, 1667, 1543, 1455, 1347, 1265, 1170, 719  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.13 (d,  $J$  = 6.8 Hz, 3H), 1.33 (d,  $J$  = 6.8 Hz, 3H), 2.87-3.05 (m, 1H), 3.87 (s, 6H), 4.33-4.45 (m, 1H), 6.63 (d,  $J$  = 8.6 Hz, 1H), 8.96 (d,  $J$  = 2.0 Hz, 2H), 9.18 (t,  $J$  = 2.0 Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  11.4 (d,  $J_{\text{C-F}}$  = 4.8 Hz), 18.4 (d,  $J_{\text{C-F}}$  = 1.9 Hz), 41.9 (d,  $J_{\text{C-F}}$  = 20.0 Hz), 47.6, 53.7, 96.9 (d,  $J_{\text{C-F}}$  = 204 Hz), 121.1, 127.1, 137.7, 148.7, 161.7, 166.0 (d,  $J_{\text{C-F}}$  = 25.7 Hz), 166.7 (d,  $J_{\text{C-F}}$  = 25.7 Hz); HRMS (ESI):  $m/z$  calculated for  $\text{C}_{16}\text{H}_{18}\text{O}_9\text{N}_3\text{FNa}^+$   $[\text{M}+\text{Na}]^+$ : 438.0919, found: 438.0920; HPLC



(chiral column: DAICEL CHIRALPAK IC; solvent: hexane/2-propanol = 2/1; flow rate: 1.0 mL/min; detection: at 254 nm):  $t_R = 11.9$  min (major) and 13.5 min (minor);  $[\alpha]_D^{22.1} -5.6$  ( $c$  1.02, acetone).

**Dimethyl 2-((4*R*,5*R*)-5-(3,5-dinitrobenzamido)octan-4-yl)-2-fluoromalonate (4da):** colorless solid; mp 103.5-106.0 °C; IR (KBr)  $\nu$  3241, 2966, 1764, 1742, 1649, 1551, 1344, 1169, 920, 729  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.93 (t,  $J = 7.8$  Hz, 3H), 0.94 (t,  $J = 7.4$  Hz, 3H), 1.30-1.69 (m, 8H), 2.77 (ddt,  $J = 28.7, 9.0, 3.1$  Hz, 1H), 3.87 (s, 3H), 3.90 (s, 3H), 4.45-4.57 (m, 1H), 6.95 (d,  $J = 9.9$  Hz, 1H), 9.01 (d,  $J = 2.0$  Hz, 1H), 9.18 (t,  $J = 2.0$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  13.7, 13.9, 19.9, 20.8, 30.3 (d,  $J_{\text{C-F}} = 3.8$  Hz), 36.0 (d,  $J_{\text{C-F}} = 1.9$  Hz), 46.2 (d,  $J_{\text{C-F}} = 19.1$  Hz), 49.9, 53.6, 53.8, 97.3 (d,  $J_{\text{C-F}} = 202$  Hz), 121.0, 127.2, 137.8, 148.6, 162.3, 166.3 (d,  $J_{\text{C-F}} = 25.7$  Hz), 167.5 (d,  $J_{\text{C-F}} = 26.7$  Hz); HRMS (ESI):  $m/z$  calculated for  $\text{C}_{20}\text{H}_{26}\text{O}_9\text{N}_3\text{FNa}^+$   $[\text{M}+\text{Na}]^+$ : 494.1545, found: 494.1541; HPLC (chiral column: DAICEL CHIRALPAK IB; solvent: hexane/2-propanol = 2/1; flow rate: 1.0 mL/min; detection: at 265 nm):  $t_R = 7.3$  min (major) and 9.4 min (minor);  $[\alpha]_D^{22.1} +8.1$  ( $c$  1.02, acetone).

**Dimethyl 2-((2*R*,3*R*)-3-(3,5-dinitrobenzamido)1,2,3,4-tetrahydronaphthalen-2-yl)-2-fluoromalonate (4ea):** colorless solid; mp 161.5-162.0 °C; IR (KBr)  $\nu$  3309, 2957, 1763, 1742, 1648, 1543, 1344, 1265, 731  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  2.82-2.96 (m, 4H), 2.98-3.17 (m, 4H), 3.24 (dd,  $J = 16.0, 5.2$  Hz, 1H), 3.81 (s, 3H), 3.92 (s, 3H), 4.64-4.75 (m, 1H), 6.79 (d,  $J = 8.6$  Hz, 1H), 7.07-7.23 (m, 4H), 8.91 (d,  $J = 2.4$  Hz, 2H), 9.15 (t,  $J = 2.4$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  29.4 (d,  $J_{\text{C-F}} = 3.6$  Hz), 36.2, 43.7 (d,  $J_{\text{C-F}} = 20.4$  Hz), 47.2 (d,  $J_{\text{C-F}} = 2.4$  Hz), 53.9, 95.9 (d,  $J_{\text{C-F}} = 206$  Hz), 121.1, 126.8, 126.9, 127.2, 128.3, 128.5, 133.5, 133.8, 137.7, 148.7, 161.8, 166.3 (d,  $J_{\text{C-F}} = 26.4$  Hz), 166.7 (d,  $J_{\text{C-F}} = 26.4$  Hz); HRMS (ESI):  $m/z$  calculated for  $\text{C}_{22}\text{H}_{20}\text{O}_9\text{N}_3\text{FNa}^+$   $[\text{M}+\text{Na}]^+$ : 512.1075, found: 512.1076; HPLC (chiral column: DAICEL CHIRALPAK IB; solvent: hexane/2-propanol = 2/1; flow rate: 1.0 mL/min; detection: at 254 nm):  $t_R = 12.9$  min (major) and 21.0 min (minor);  $[\alpha]_D^{23.4} -39.4$  ( $c$  0.64, acetone).

**Dimethyl 2-((1*R*,6*R*)-6-(3,5-dinitrobenzamido)cyclohex-3-en-1-yl)-2-fluoromalonate (4fa):** colorless solid; mp 182.0-184.0 °C; IR (KBr)  $\nu$  3266, 3100, 1762, 1647, 1542, 1343, 1298, 1152, 719  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  2.08-2.23 (m, 2H), 2.36-2.49 (m, 1H), 2.66 (dd,  $J = 16.6, 4.9$  Hz, 1H), 3.02 (dtd,  $J = 24.0, 10.8, 5.6$ , 1H), 3.79 (s, 3H), 3.90 (s, 3H), 4.41-4.52 (m, 1H), 5.66-5.73 (m, 2H), 6.73 (d,  $J = 9.0$  Hz, 1H), 8.95 (d,  $J = 2.4$  Hz, 2H), 9.19 (t,  $J = 2.4$  Hz, 1H);  $^{13}\text{C}$  NMR (acetone- $d_6$ , 100 MHz)  $\delta$  27.1, 32.9, 43.5 (d,  $J_{\text{C-F}} = 20.5$  Hz), 46.7 (d,  $J_{\text{C-F}} = 3.0$  Hz), 53.7, 96.3 (d,  $J_{\text{C-F}} = 206$  Hz), 121.7, 125.7, 128.1, 138.5, 149.6, 162.5, 166.6 (d,  $J_{\text{C-F}} = 26.6$  Hz), 167.3 (d,  $J_{\text{C-F}} = 25.8$  Hz); HRMS (ESI):  $m/z$  calculated for  $\text{C}_{18}\text{H}_{18}\text{O}_9\text{N}_3\text{FNa}^+$   $[\text{M}+\text{Na}]^+$ : 462.0921, found: 462.0919; HPLC (chiral column: DAICEL CHIRALPAK

IC; solvent: hexane/2-propanol = 2/1; flow rate: 1.0 mL/min; detection: at 254 nm):  $t_R$  = 19.0 min (major) and 25.2 min (minor);  $[\alpha]_D^{22.7}$   $-52.9$  ( $c$  0.98, acetone).

**Methyl 2-((1*R*,2*R*)-2-(3,5-dinitrobenzamido)cyclohexyl)-2-fluoroacetate (7aa):** To a solution **4aa** (177.3 mg, 0.40 mmol) in DMSO (0.6 mL) in a test tube were added H<sub>2</sub>O (8  $\mu$ L, 0.44 mmol, 1.1 equiv) and LiI (112 mg, 0.84 mmol, 2.1 equiv), and the reaction mixture was stirred for 1 h at 130 °C. After cooling down to room temperature, the reaction mixture was diluted with water, extracted with CH<sub>2</sub>Cl<sub>2</sub> (x 3). Combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtration and evaporation. The residue was purified by silica gel column chromatography (hexane: AcOEt = 4:1 to 2:1) to afford **7aa** (142 mg, 93% yield) as a *ca.* 1:1 mixture of inseparable diastereomers; colorless solid; IR (KBr)  $\nu$  3268, 2943, 1764, 1742, 1651, 1540, 1343, 1281, 1158, 701 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  1.22-1.59 (m, 8H), 1.67-1.75 (m, 3H), 1.80-1.90 (m, 5H), 2.03-2.36 (m, 4H), 3.68 (s, 3H), 3.79 (s, 3H), 4.04-4.23 (m, 2H), 4.89 (dd,  $J$  = 47.3, 3.2 Hz, 1H), 5.06 (dd,  $J$  = 48.4, 1.4 Hz, 1H), 6.68 (d,  $J$  = 8.6 Hz, 1H), 6.84 (d,  $J$  = 8.6 Hz, 1H), 8.96 (d,  $J$  = 1.7 Hz, 2H), 9.01 (d,  $J$  = 2.3 Hz, 2H), 9.11-9.19 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  24.8 (d,  $J_{C-F}$  = 3.6 Hz), 25.0, 25.1, 25.3 (d,  $J_{C-F}$  = 4.8 Hz), 28.5, 33.3, 33.4, 44.5 (d,  $J_{C-F}$  = 19.2 Hz), 45.4 (d,  $J_{C-F}$  = 19.2 Hz), 50.1, 52.5, 52.6, 89.0 (d,  $J_{C-F}$  = 190 Hz), 91.0 (d,  $J_{C-F}$  = 185 Hz), 121.0, 121.1, 127.2, 127.3, 137.9, 148.6, 161.9, 162.4, 170.1 (d,  $J_{C-F}$  = 24.0 Hz), 170.3 (d,  $J_{C-F}$  = 24.0 Hz); HRMS (ESI):  $m/z$  calculated for C<sub>16</sub>H<sub>18</sub>O<sub>7</sub>N<sub>3</sub>FN<sup>+</sup> [M+Na]<sup>+</sup>: 406.1021, found: 406.1018.

**Methyl 2-((1*R*,2*R*)-2-((*tert*-butoxycarbonyl)amino)cyclohexyl)-2-fluoroacetate (8aa):** To a solution of **7aa** (115 mg, 0.30 mmol, diastereomixture) in THF (0.6 mL) were added Boc<sub>2</sub>O (589 mg, 2.70 mmol, 9 equiv), Et<sub>3</sub>N (46  $\mu$ L, 0.33 mmol, 1.1 equiv) and DMAP (7.3 mg, 0.06 mmol, 0.20 equiv), and the mixture stirred at room temperature for 24 h. The volatile material was removed under reduced pressure and the residue was purified by silica gel flash column chromatography (hexane: AcOEt = 10:1) to afford *N*-Boc protected intermediate as an amorphous solid. The intermediate was dissolved in anhydrous MeOH (1.0 mL), and NaOMe (1.0 M MeOH solution, 0.33 mL, 0.33 mmol, 1.1 equiv) was added at room temperature. The resulting mixture was stirred for 1.0 h at room temperature. The reaction was quenched with citric acid (120 mg, 0.62 mmol, 2.1 equiv) and then the volatile material was removed under reduced pressure. The residue was taken up in H<sub>2</sub>O, and the organic material was extracted with CH<sub>2</sub>Cl<sub>2</sub> (x 3). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane:CH<sub>2</sub>Cl<sub>2</sub>:AcOEt = 8:9:1) to afford **8aa** (68.5 mg, 79% yield in 2 steps) as a *ca.* 2:1 mixture of inseparable diastereomers; colorless solid; IR (KBr)  $\nu$  3384, 2979, 2936, 2858, 1748, 1699, 1523, 1234, 1175 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) major isomer;  $\delta$  1.11-1.34 (m, 3H), 1.34-1.62 (m, 1H), 1.43 (s, 9H), 1.67-1.88 (m, 3H), 1.90-2.12 (m, 2H), 3.38-3.70 (m, 1H), 3.81 (s, 3H),

4.35 (d,  $J = 10.0$  Hz, 1H), 4.80 (dd,  $J = 47.6, 2.2$  Hz, 1H), minor isomer; 1.11-1.34 (m, 3H), 1.34-1.62 (m, 1H), 1.44 (s, 9H) 1.67-1.88 (m, 3H), 1.90-2.12 (m, 2H), 3.38-3.70 (m, 1H), 3.80 (s, 3H), 4.54 (d,  $J = 9.6$  Hz, 1H), 5.13 (brd,  $J = 48.9$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  24.9, 25.0, 28.3, 28.6, 34.1, 45.5 (d,  $J_{\text{C-F}} = 19.7$  Hz), 45.9 (d,  $J_{\text{C-F}} = 21.6$  Hz), 48.8 (d,  $J_{\text{C-F}} = 4.7$  Hz), 49.3, 52.3, 79.2, 79.4, 88.1 (d,  $J_{\text{C-F}} = 189$  Hz), 90.3 (d,  $J_{\text{C-F}} = 190$  Hz), 154.7, 155.2, 170.4, 170.7; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{14}\text{H}_{24}\text{O}_4\text{NFNa}^+$   $[\text{M}+\text{Na}]^+$ : 312.1582, found: 312.1578.

**(3*S*,3*aR*,7*aR*)-3-Fluorooctahydro-2*H*-indol-2-one (10aa) & (3*R*,3*aR*,7*aR*)-3-fluorooctahydro-2*H*-indol-2-one (10'aa):** **8aa** (44.5 mg, 0.15 mmol, *ca.* 2:1 diastereomixture) was stirred with 4 M *aq.* HCl (2.0 mL) at 90 °C for 24 h. The reaction mixture was concentrated under vacuum to afford crude **9aa**. The resulting crude solid **9aa** was dissolved in  $\text{CH}_2\text{Cl}_2$  (20 mL) and 2-chloro-1-methylpyridinium iodide (157.4 mg, 0.62 mmol, 4.0 equiv) was added, then  $\text{Et}_3\text{N}$  (172  $\mu\text{L}$ , 1.23 mmol, 8.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) was slowly added over 2 h. The reaction mixture was refluxed for 48 h with the exclusion of light, then cooled to room temperature and concentrated. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1:1 to 1:0) to afford lactams **10aa** (5.9 mg, 24%) and **10'aa** (10.7 mg, 44%); **10aa**; colorless solid; IR (KBr)  $\nu$  3235, 3140, 2933, 2864, 1716, 1278, 1091, 970, 937, 748  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.28-1.48 (m, 4H), 1.80-2.16 (m, 5H), 2.92-3.08 (m, 1H), 4.77 (dd,  $J = 53.0, 10.9$  Hz, 1H), 6.73 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  23.9, 25.2, 26.0, 30.7, 51.0 (d,  $J_{\text{C-F}} = 17.2$  Hz), 53.6 (d,  $J_{\text{C-F}} = 9.5$  Hz), 91.8 (d,  $J_{\text{C-F}} = 195$  Hz), 173.0 (d,  $J_{\text{C-F}} = 21.9$  Hz); HRMS (ESI):  $m/z$  calculated for  $\text{C}_8\text{H}_{12}\text{ONFNa}^+$   $[\text{M}+\text{Na}]^+$ : 180.0795, found: 180.0795;  $[\alpha]_{\text{D}}^{22.7} -54.8$  ( $c = 0.65$ ,  $\text{CHCl}_3$ ); **10'aa**; colorless solid; IR (KBr)  $\nu$  3266, 3941, 3862, 1719, 1688, 1445, 1291, 1124, 1087, 746  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.22-1.47 (m, 3H), 1.51-1.76 (m, 2H), 1.78-1.97 (m, 3H), 2.05-2.16 (m, 1H), 3.37-3.53 (m, 1H), 4.69 (dd,  $J = 53.5, 3.6$  Hz, 1H), 6.91 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  22.6 (d,  $J_{\text{C-F}} = 2.9$  Hz), 24.0, 25.6, 30.7, 49.5 (d,  $J_{\text{C-F}} = 20.0$  Hz), 57.3, 90.9 (d,  $J_{\text{C-F}} = 181$  Hz), 172.7 (d,  $J_{\text{C-F}} = 17.2$  Hz); HRMS (ESI):  $m/z$  calculated for  $\text{C}_8\text{H}_{12}\text{ONFNa}^+$   $[\text{M}+\text{Na}]^+$ : 180.0795, found: 180.0796;  $[\alpha]_{\text{D}}^{22.4} +111.4$  ( $c = 0.84$ ,  $\text{CHCl}_3$ ).

## ACKNOWLEDGEMENTS

This research was supported in part by a Grant-in-Aid from the Ministry of Education, Science, Sports and Culture, Japan, JSPS KAKENHI Grant Number JP15H05802 in Precisely Designed Catalysts with Customized Scaffolding, JST ACT-C Grant Number JPMJCR12Z6, Japan, and Toray Science Foundation. We thank Prof. Motomu Kanai at the University of Tokyo for his kind assistance and discussion at the initial stage of this work.

## REFERENCES AND NOTES

- For reviews, see: (a) S. Purser, P. R. Moore, S. Swallow, and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (b) K. Muller, C. Faeh, and F. Diederich, *Science*, 2007, **317**, 1881; (c) K. L. Kirk, *Org. Process Res. Dev.*, 2008, **12**, 305; (d) C. Isanbor and D. O'Hagan, *J. Fluorine Chem.*, 2006, **127**, 303; (e) J.-P. Begue and D. Bonnet-Delpon, *J. Fluorine Chem.*, 2006, **127**, 992.
- F. Lovering, J. Bikker, and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752.
- For reviews, see: (a) X. Yang, T. Wu, R. J. Phipps, and F. D. Toste, *Chem. Rev.*, 2015, **115**, 826; (b) C. N. Neumann and T. Ritter, *Angew. Chem. Int. Ed.*, 2015, **54**, 3216; (c) V. Bizet, T. Besset, J. A. Ma, and D. Cahard, *Curr. Top. Med. Chem.*, 2014, **14**, 901; (d) J. R. Wolstenhulme and V. Gouverneur, *Acc. Chem. Res.*, 2014, **47**, 3560; (e) D. Cahard, X. Xu, S. Couve-Bonnaire, and X. Pannecoucke, *Chem. Soc. Rev.*, 2010, **39**, 558; (f) R. Smits, C. D. Cadicamo, K. Burger, and B. Kokschi, *Chem. Soc. Rev.*, 2008, **37**, 1727; (g) V. A. Brunet and D. O'Hagan, *Angew. Chem. Int. Ed.*, 2008, **47**, 1179; (h) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2008, **108**, PR1; (i) N. Shibata, T. Ishimaru, S. Nakamura, and T. Toru, *J. Fluorine Chem.*, 2007, **128**, 469; (j) M. Oestreich, *Angew. Chem. Int. Ed.*, 2005, **44**, 2324; (k) G. K. S. Prakash and P. Beier, *Angew. Chem. Int. Ed.*, 2006, **45**, 2172; (l) P. M. Pihko, *Angew. Chem. Int. Ed.*, 2006, **45**, 544; (m) H. Ibrahim and A. Togni, *Chem. Commun.*, 2004, 1147.
- Reviews on catalytic asymmetric reactions using organofluoro nucleophiles: (a) A. Harsanyi and G. Sandford, *Org. Process Res. Dev.*, 2014, **18**, 981; (b) Y. Zhao, Y. Pan, S.-B. O. Sim, and C. H. Tan, *Org. Biomol. Chem.*, 2012, **10**, 479; (c) K. Shibatomi, *Synthesis*, 2010, 2679; (d) K. Mikami, Y. Itoh, and M. Yamanaka, *Chem. Rev.*, 2004, **104**, 1; For related works using organofluoro electrophiles, see: (e) J. Nie, H.-C. Guo, D. Cahard, and J.-A. Ma, *Chem. Rev.*, 2011, **111**, 455.
- For selected recent examples using organofluoro nucleophiles other than fluoromalonates, see: (a) M. Nakamura, A. Hajra, K. Endo, and E. Nakamura, *Angew. Chem. Int. Ed.*, 2005, **44**, 7248; (b) T. Fukuzumi, N. Shibata, M. Sugiura, H. Yasui, S. Nakamura, and T. Toru, *Angew. Chem. Int. Ed.*, 2006, **45**, 4973; (c) S. Mizuta, N. Shibata, Y. Goto, T. Furukawa, S. Nakamura, and T. Toru, *J. Am. Chem. Soc.*, 2007, **129**, 6394; (d) T. Furukawa, N. Shibata, S. Mizuta, S. Nakamura, T. Toru, and M. Shiro, *Angew. Chem. Int. Ed.*, 2008, **47**, 8051; (e) R. He, X. Wang, T. Hashimoto, and K. Maruoka, *Angew. Chem. Int. Ed.*, 2008, **47**, 9466; (f) C. Ding and K. Maruoka, *Synlett*, 2009, 664; (g) Z. Jiang, Y. Pan, Y. Zhao, T. Ma, R. Lee, Y. Yang, K.-W. Huang, M. W. Wong, and C.-H. Tan, *Angew. Chem. Int. Ed.*, 2009, **48**, 3627; (h) X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, and Y. Lu, *Angew. Chem. Int. Ed.*, 2009, **48**, 7604; (i) F. Ullah, G.-L. Zhao, L. Deiana, M. Zhu, P. Dziedzic, I. Ibrahim, P. Hammar, J. Sun, and A. Córdova, *Chem. Eur. J.*, 2009, **15**, 10013; (j) Y. Pan, Y. Zhao, T. Ma, Y. Yang, H. Liu, Z. Jiang, and C.-H. Tan, *Chem. Eur. J.*, 2010, **16**, 779; (k) W. Kashikura, K. Mori, and

- T. Akiyama, [Org. Lett., 2011, 13, 1860](#); (l) S. J. Yoon, Y. K. Kang, and D. Y. Kim, [Synlett, 2011, 420](#); (m) Y. K. Kang and D. Y. Kim, [Tetrahedron Lett., 2011, 52, 2356](#); (n) S.-L. Zhang, H.-X. Xie, J. Zhu, H. Li, X.-S. Zhang, J. Li, and W. Wang, [Nat. Commun., 2011, 2, 211 \[DOI: 10.1038/ncomms1214\]](#); (o) L. Yin, L. Brewitz, N. Kumagai, and M. Shibasaki, [J. Am. Chem. Soc., 2014, 136, 17958](#); (p) J. Kwiatkowski and Y. Lu, [Asian J. Org. Chem., 2014, 3, 458](#); (q) M. Yoshida, A. Kubara, Y. Nagasawa, S. Hara, and M. Yamanaka, [Asian J. Org. Chem., 2014, 3, 523](#); (r) L. Brewitz, F. A. Arteaga, L. Yin, K. Alagiri, N. Kumagai, and M. Shibasaki, [J. Am. Chem. Soc., 2015, 137, 15929](#); (s) J. Saadi and H. Wennemers, [Nat. Chem., 2016, 8, 276](#); (t) E. Cosimi, O. D. Engl, J. Saadi, M.-O. Ebert, and H. Wennemers, [Angew. Chem. Int. Ed., 2016, 55, 13127](#); (u) E. Cosimi, J. Saadi, and H. Wennemers, [Org. Lett., 2016, 18, 6014](#); (v) L. Brewitz, N. Kumagai, and M. Shibasaki, [J. Fluorine Chem., 2017, 194, 1](#); For other early examples, see reviews in ref. 4.
6. (a) D. Y. Kim, S. M. Kim, K. O. Koh, J. Y. Mang, and K. Lee, [Bull. Korean Chem. Soc., 2003, 24, 1425](#); (b) M. J. Cho, M. G. Cho, S. C. Huh, S. M. Kim, K. Lee, K. O. Koh, J. Y. Mang, and D. Y. Kim, [Bull. Korean Chem. Soc., 2006, 27, 857](#); (c) P. J. Nichols, J. A. DeMattei, B. R. Barnett, N. A. LeFur, T.-H. Chuang, A. D. Piscopio, and K. Koch, [Org. Lett., 2006, 8, 1495](#); (d) H. Li, L. Zu, H. Xie, and W. Wang, [Synthesis, 2009, 1525](#); (e) B. K. Kwon, S. M. Kim, and D. Y. Kim, [J. Fluorine Chem., 2009, 130, 759](#); (f) X. Companyó, M. Hejnová, M. Kamlar, J. Vesely, A. Moyano, and R. Rios, [Tetrahedron Lett., 2009, 50, 5021](#); (g) S. H. Kang and D. Y. Kim, [Bull. Korean Chem. Soc., 2009, 30, 1439](#); (h) H. Li, Y. Ji, J. Li, S. Zhang, C. Yu, and W. Wang, [Science: China Chem., 2010, 53, 135](#); (i) D. Cao, G. Fang, J. Zhang, H. Wang, C. Zheng, and G. Zhao, [J. Org. Chem., 2016, 81, 9973](#).
7. (a) J. H. Lee and D. Y. Kim, [Synthesis, 2010, 1860](#); (b) M. Hatano, T. Horibe, and K. Ishihara, [Org. Lett., 2010, 12, 3502](#); (c) H.-Y. Wang, K. Zhang, C.-W. Zheng, Z. Chai, D.-D. Cao, J.-X. Zhang, and G. Zhao, [Angew. Chem. Int. Ed., 2015, 54, 1775](#).
8. For related catalytic asymmetric desymmetrization of aziridines via nucleophilic fluorination, see: J. A. Kalow and A. G. Doyle, [Tetrahedron, 2013, 69, 5702](#).
9. Reviews on dinuclear Schiff base catalysis: (a) S. Matsunaga and M. Shibasaki, [Synthesis, 2014, 45, 421](#); (b) S. Matsunaga and M. Shibasaki, [Chem. Commun., 2014, 50, 1044](#); (c) N. Kumagai, M. Kanai, and H. Sasai, [ACS Catal., 2016, 6, 4699](#).
10. For reviews of enantioselective desymmetrization of aziridines, see: (a) C. Schneider, [Angew. Chem. Int. Ed., 2009, 48, 2082](#); (b) P.-A. Wang, [Beilstein J. Org. Chem., 2013, 9, 1677](#).
11. Y. Xu, L. Lin, M. Kanai, S. Matsunaga, and M. Shibasaki, [J. Am. Chem. Soc., 2011, 133, 5791](#).
12. For related works using enolates as nucleophiles: (a) K. Ohmatsu, Y. Ando, and T. Ooi, [J. Am. Chem. Soc., 2013, 135, 18706](#); (b) Y. Xu, K. Kaneko, M. Kanai, M. Shibasaki, and S. Matsunaga, [J. Am.](#)

- [Chem. Soc.](#), 2014, **136**, 9190; (c) D. Yang, L. Wang, F. Han, D. Li, D. Zhao, and R. Wang, [Angew. Chem. Int. Ed.](#), 2015, **54**, 2185; (d) L. Wang, D. Yang, D. Li, and R. Wang, [Org. Lett.](#), 2015, **17**, 3004; (e) D. Li, L. Wang, D. Yang, B. Zhang, and R. Wang, [ACS Catal.](#), 2015, **5**, 7432; (f) L. Wang, D. Li, D. Yang, K. Wang, J. Wang, P. Wang, W. Su, and R. Wang, [Chem. Asian J.](#), 2016, **11**, 691; (g) D. Li, Y. Wang, L. Wang, J. Wang, P. Wang, K. Wang, L. Lin, D. Liu, X. Jiang, and D. Yang, [Chem. Commun.](#), 2016, **52**, 9640; (h) N. Shiomi, M. Kuroda, and S. Nakamura, [Chem. Commun.](#), 2017, **53**, 1817; For other examples, see reviews in ref. 10.
13. Evaluation of the relative Lewis acidity of rare earth metals: H. Tsuruta, K. Yamaguchi, and T. Imamoto, [Chem. Commun.](#), 1999, 1703.
  14. At the stage of initial screening, other *N*-substituents gave only unsatisfactory results. When changing the Ar group of aziridine **2a** from 3,5-(NO<sub>2</sub>)<sub>2</sub>-C<sub>6</sub>H<sub>3</sub> into either 4-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub> or 2-pyridyl, undesired oxazoline formation predominantly proceeded. *N*-Ts-aziridine and *N*-3,5-dimethoxybenzoylaziridine resulted in no reaction under the present bimetallic catalysis.
  15. (a) T. Mukaiyama, M. Usui, and K. Saigo, [Chem. Lett.](#), 1976, 49; Mukaiyama's reagent in the synthesis of *trans*-fused bicyclic  $\gamma$ -lactams, see: (b) H. A. Kelly, R. Bolton, S. A. Brown, S. J. Coote, M. Dowle, U. Dyer, H. Finch, D. Golding, A. Lowdon, J. McLaren, J. G. Montana, M. R. Owen, N. A. Pegg, B. C. Ross, R. Thomas, and D. A. Walker, [Tetrahedron Lett.](#), 1998, **39**, 6979; (c) M. F. Z. Page, S. S. Jalisatgi, A. Maderna, and M. F. Hawthorne, [Synthesis](#), 2008, 555.