HETEROCYCLES, Vol. 99, No. 2, 2019, pp. 1398 - 1411. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 21st September, 2018, Accepted, 16th November, 2018, Published online, 13th February, 2019
DOI: 10.3987/COM-18-S(F)87

ASYMMETRIC SYNTHESIS OF *t*-BUTYL 3-ALKYL-OXINDOLE-3-CARBOXYLATES VIA CHIRAL PHOSPHORIC ACID-CATALYZED DESYMMETRIZATION OF DI-*t*-BUTYL 2-ALKYL-2-(2-AMINOPHENYL)MALONATES

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Abstract – We describe the asymmetric desymmetrization of di-*t*-butyl 2-alkyl-2-(2-aminophenyl)malonates to prepare enantioenriched *t*-butyl 3-alkyl-oxindole-3-carboxylates using (*S*)-TRIP, a chiral phosphoric acid. Optimization study increased the enantioselectivity up to 66% ee.

Chiral 3,3-disubstituted oxindoles are often used for synthesis of natural products or bioactive compounds.[1] In particular, asymmetric synthesis of alkyl 3-alkyl-oxindole-3-carboxylates has attracted a great deal of attention due to chirality of these compounds, which often influences biological activity.[2] For example, Kozlowski and co-workers reported asymmetric synthesis of oxindoles using Claisen rearrengement.[3] Furthermore, Park and co-workers reported the use of enantioselective alkylation at the α-position of malonates followed by lactamization.[4] Although cyclization reaction of dialkyl 2-alkyl-2-(2-aminophenyl)malonates is one of the most frequently used methodologies for the synthesis of alkyl 3-alkyl-oxindole-3-carboxylates,[5] there is no enantioselective synthesis of alkyl 3-alkyl-oxindole-3-carboxylates using asymmetric desymmetrization of dialkyl 2-alkyl-2-(2-aminophenyl)malonates. Therefore, it is important to develop a novel effective methodology toward the synthesis of the desired oxindoles via asymmetric desymmetrization of dialkyl 2-alkyl-2-(2-aminophenyl)malonates, which can concisely be synthesized from the cost-effective dialkyl malonates. Here, we describe the asymmetric synthesis of oxindole **1** using chiral phosphoric acid-catalyzed asymmetric desymmetrization of the symmetric di-*t*-butyl malonate **2** (Figure 1). To the best of our knowledge, this is the first report describing the synthesis of chiral lactams via enantioselective desymmetrization.

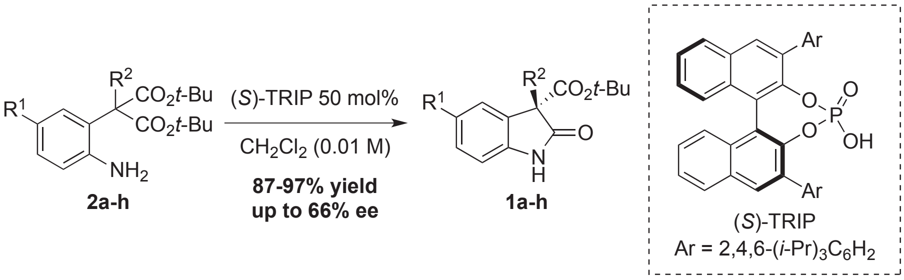
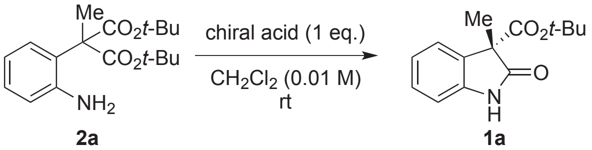
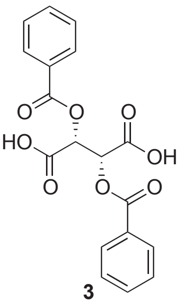


Figure 1. Asymmetric synthesis of *t*-butyl 3-alkyl-oxindole-3-carboxylates using chiral phosphoric acid-catalyzed asymmetric desymmetrization

Table 1. Screening of chiral Brønsted acids for desymmetrization



2a **1a**



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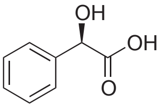

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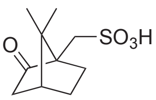

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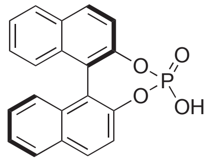

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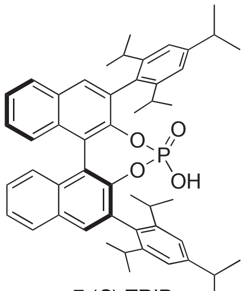


7:(*S*)-TRIP

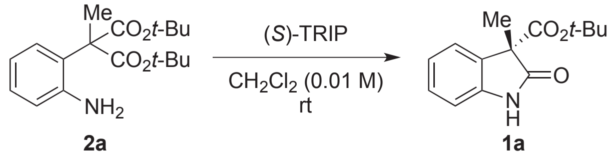
Entry	Acid	Time (h)	Yield (%)	ee[a] (%)
1	**3**	24	92	5
2	**4**	36	94	11
3	**5**	4	88	−1
4	**6**	4	quant.	10
5	**7**	0.5	90	45

[a] Enantiomeric excess of isolated **1a** was determined by chiral HPLC analysis.

In our program to develop efficient synthesis of 3,3-disubstituted oxindoles, we have used Brønsted acids-catalyzed cyclization of di-*t*-butyl 2-alkyl-2-(2-aminophenyl)malonates to obtain *t*-butyl 3-alkyl-oxindole-3-carboxylates.[6] Petersen's report that chiral Brønsted acid recognizes one of the equivalent carbonyl group and leads to cyclization[7] led us to hypothesize that the use of chiral Brønsted acids produces chiral *t*-butyl 3-alkyl-oxindole-3-carboxylates.

First, we screened several chiral Brønsted acids based on our previous finding that Brønsted acids mediated desymmetrization of the malonate **2**, effectively affording the oxindole **1**. To avoid intermolecular interaction, we carried out these reactions under relatively low concentrations (0.01 M).[8] Based on our report that carboxylic acids, sulfonic acids and phosphoric acids accelerate the cyclization reaction, we picked up the commercially available chiral carboxylic acids **3** and **4**, the (+)-10-camphorsulfonic acid **5**, and the BINOL-phosphoric acids **6** and **7**. The results of our initial screening with these acids are summarized in Table 1. The reactions using chiral carboxylic acids **3** and **4** were completed in 24–36 hours (entries 1 and 2), yielding oxindole **1a**. On the other hand, the sulfonic acid **5** and the phosphoric acids **6** and **7** afforded oxindole **1a** within 4 hours (entries 3–5). Of these reactions, addition of (*S*)-TRIP (**7**) quickly (within 0.5 hours) accomplished oxindole cyclization to afford compound **1a** in 90% yield, 45% ee (entry 5).

Table 2. Effect of catalyst loading



Entry	(*S*)-TRIP (mol%)	Time	Product ratio (**2a** / **1a**)	Isolated yield (%)	ee[c] (%)
1	100	0.5 h	0 / 100[a]	90	45
2	50	2 h	0 / 100[a]	87	49
3	20	7 days	0 / 100[a]	90	47
4	5	7 days	50 / 50[b]	52	41 [41]

[a] Consumption of **2a** was confirmed by TLC analysis.

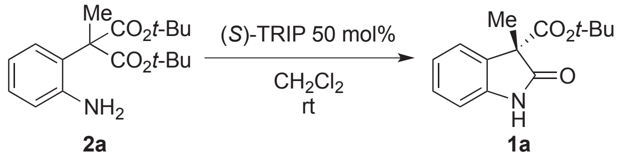
[b] Product ratio between **1a** and **2a** was determined by ^{1}H NMR analysis of the reaction mixture.

[c] Enantiomeric excess of isolated **1a** was determined by chiral HPLC. The number in straight parentheses represents enantiomeric excess of reaction mixture.

Second, we investigated the appropriate equivalent ratio of (*S*)-TRIP (Table 2). Asymmetric desymmetrization using (*S*)-TRIP afforded a lactone featuring high optical purity, as well as high yield, even at a concentration as low as 20 mol%.[7] However, reducing (*S*)-TRIP load to 5 mol% significantly decreased reactivity though without affecting enantioselectivity (entries 1–4).

Third, we tried to optimize reagents concentrations. The results are shown in Table 3. Increase in the reaction concentration from 0.01 M to 0.3 M led to shortening of the reaction time and decrease of enantioselectivity (entries 1–4). Furthermore, decrease of the reaction concentration from 0.01 M to 0.003 M slightly reduced enantioselectivity (entry 5). Thus, we chose 0.01 M for subsequent reactions.

Table 3. Effect of reaction concentration.

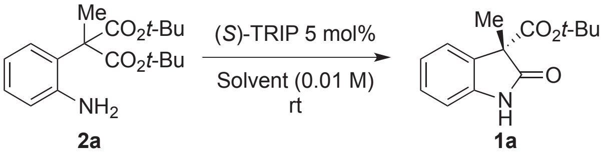


Entry	Concentration (M)	Time	Isolated yield (%)	ee[a] (%)
1	0.01	2 h	87	49
2	0.03	1 h	96	39
3	0.1	30 min	95	34
4	0.3	10 min	99	21
5	0.003	3 h	89	43

[a] Enantiomeric excess of isolated **1a** was determined by chiral HPLC.

Fourth, we optimized the solvents in the reaction as shown in Table 4. Our previous report shows that cyclization of **2a** to ***rac*-1a** in methanol increased reactivity.[6] Although the cyclization of **2a** increased in methanol, enantioselectivity was completely canceled (entry 2). Likewise, polar aprotic solvents, such as acetonitrile and ethyl acetate, did not induce enantioselective cyclization (entries 3 and 4). Additionally, both conversion yield and ee value were slightly decreased using toluene as solvent (entry 5). Based on these results, we chose dichloromethane as optimal solvent for further investigation.

Table 4. Effect of solvents



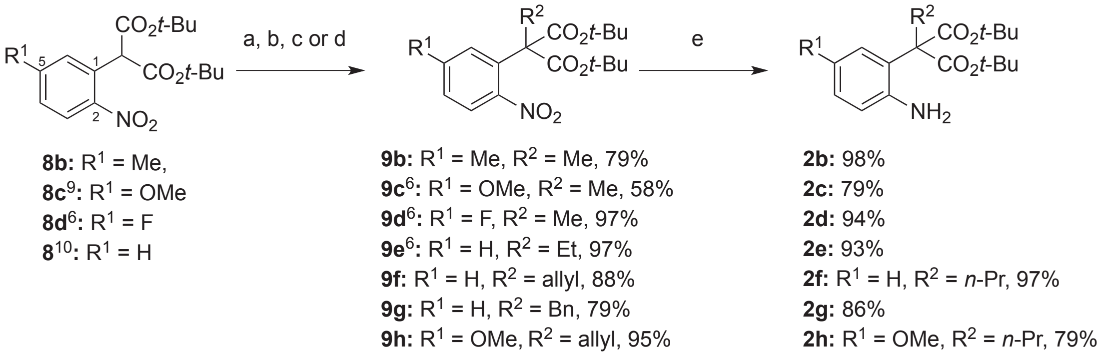
Entry	Solvent	Time	Product ratio (**2a** / **1a**)	Recovered **2a** (%)	Isolated yield (%)	ee[c] (%)
1	CH_2Cl_2	7 days	50 / 50[a]	39	52	41 [41]
2	MeOH	24 h	0 / 100[b]	0	94	−6
3	MeCN	7 days	0 / 100[b]	0	94	14
4	EtOAc	7 days	26 / 74[a]	24	62	−5 [−7]
5	PhMe	7 days	67 / 33[a]	55	33	20 [30]

[a] Product ratio between **1a** and **2a** was determined by ^{1}H NMR analysis of the reaction mixture.

[b] Consumption of **2a** was confirmed by TLC analysis.

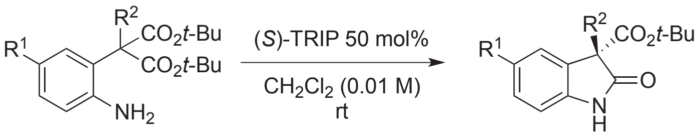
[c] Enantiomeric excess of isolated **1a** was determined by chiral HPLC analysis. Numbers in straight parentheses represent enantiomeric excess of reaction mixture.

Next, we extended the above findings to synthesize the substituted oxindoles **1b**–**1h** (Table 5). The substituted malonates **2b**–**2h** were prepared as described in Scheme 1. Replacement of the hydrogen atom at the *p*-position of the benzene ring by a methyl group (**2b**), a methoxy group (**2c**) or a fluoro group (**2d**) afforded the oxindoles **1b**, **1c** and **1d** with 57, 61 and 53% ee, respectively (entries 2–4). Replacement of the methyl group by an ethyl group (**2e**), a propyl group (**2f**) and a benzyl group (**2g**) increased enantioselectivity (60–62% ee, entries 5–7). Simultaneous introduction of the methoxy group (at the 5-position) and the propyl group (at the α-position) (**2h**) slightly increased enantioselectivity (66% ee, entry 8). The absolute configurations of **1g**[4a] and **1h**[4b] were determined as *S* by comparison with reported compounds.



Scheme 1. Synthesis of **2b–h**. Reagents and conditions: (a) MeI, K_2CO_3, DMF, rt; (b) EtI, NaH, DMF, 70 °C; (c) allyl bromide, K_2CO_3, DMF, rt; (d) benzyl bromide, K_2CO_3, DMF, rt; (e) Pd/C, H_2, MeOH, 0 °C.

Table 5. Effect of various substituents



2a-h **1a-h**

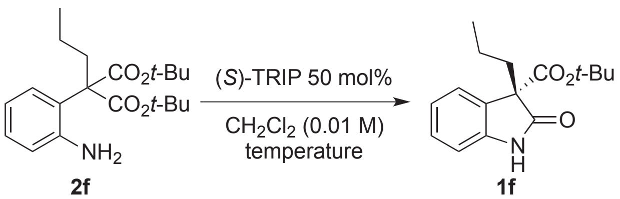
Entry	Substrate	R^1	R^2	Time^a (h)	Isolated yield (%)	ee^b (%)
1	**2a**	H	Me	2	87	49
2	**2b**	Me	Me	1	92	57
3	**2c**	OMe	Me	1	95	61
4	**2d**	F	Me	1	95	53
5	**2e**	H	Et	1	95	62
6	**2f**	H	*n*-Pr	1	95	62
7	**2g**	H	Bn	1	92	60
8	**2h**	OMe	*n*-Pr	1	97	66

[a] Consumption of **2a**–**h** was confirmed by TLC analysis.

[b] Enantiomeric excess of isolated **1a**–**h** was determined by chiral HPLC analysis.

Subsequently, we challenged further optimization of the reaction temperature to increase cyclization enantioselectivity (Table 6). Compound **2f** was then subjected to (*S*)-TRIP at low temperatures. Lowering the reaction temperature from room temperature to 0 °C or −20 °C decreased the reactivity without affecting enantioselectivity (entries 1–3).

Table 6. Effect of reaction temperature



Entry	Temperature	Time[a]	Yield (%)	ee[b] (%)
1	rt	1 h	90	62
2	0 °C	4 h	93	64
3	−20 °C	24 h	95	62

[a] Consumption of **2f** was confirmed by TLC analysis.
[b] Enantiomeric excess of isolated **1f** was determined by chiral HPLC analysis.

Based on the above results and the stereochemical outcome of the desymmetrization reaction, we proposed a potential transition state for lactamization (Figure 2). Initially, compound **2** and (*S*)-TRIP form two transition state complexes, **TS (*S*)-1** and **TS (*R*)-1.** As steric repulsion between the alkyl moiety on the oxindole and the aromatic ring of (*S*)-TRIP is unfavorable in the case of **TS (*R*)-1** as compared with in **TS (*S*)-1**, **(*S*)-1** was favorably produced.

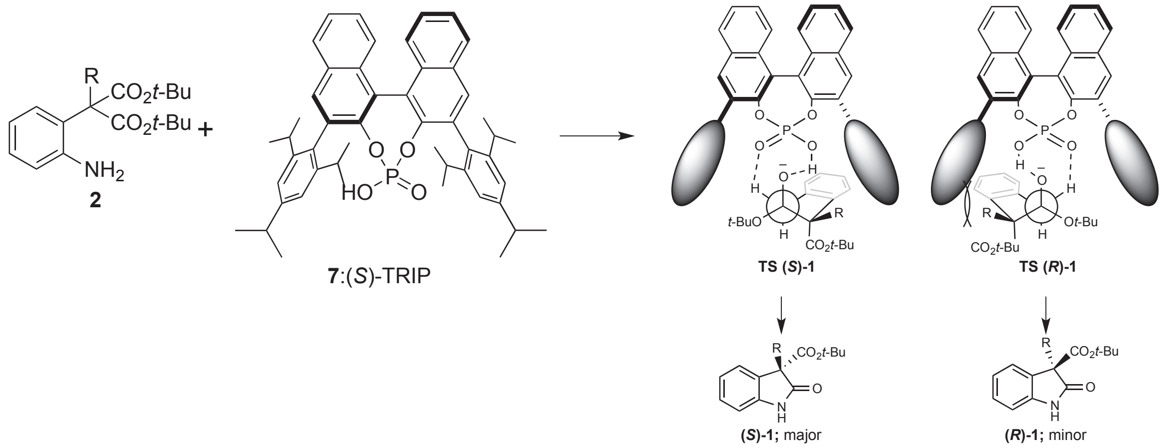


Figure 2. Potential transition state of lactamization

In summary, asymmetric desymmetrization of the di-*t*-butyl 2-methyl-2-(2-aminophenyl)malonate **2a** using (*S*)-TRIP afforded the chiral *t*-butyl 3-methyl-oxindole-3-carboxylate **1a**. Introduction of larger substituents, such as ethyl, propyl and benzyl groups, successfully increased enantioselectivity. In addition, optimization of the reaction conditions increased enantioselectivity up to 66% ee. This is the first report describing the asymmetric synthesis of oxindole **1** using enantioselective desymmetrization of di-*t*-butyl 2-methyl-2-(2-aminophenyl)malonates. We propose the mechanism of this reaction based on determining the absolute configuration of the (*S*)-TRIP-produced compound **1g** and **1h**.

EXPERIMENTAL

Melting points were recorded on Stanford Research systems MPA100 OptiMelt Automated Melting Point System and are uncorrected. IR spectra were recorded on Shimadzu IRPrestige-21. Optical rotation values were recorded on Jasco P-1020 Polarimeter. ^{1}H NMR spectra were recorded at 400 MHz with JEOL AL-400 or JEOL ECS-400 spectrometer. ^{13}C NMR spectra were recorded at 100 MHz with JEOL AL-400 or JEOL ECS-400 spectrometer. Chemical shifts (δ) are expressed in parts per million with reference to solvent signals [^{1}H NMR: $CDCl_3$ (7.26), DMSO-d_6 (2.50), ^{13}C NMR: $CDCl_3$ (77.0), DMSO-d_6 (39.5)]. Signal patterns are indicated as br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High resolution MS spectra were recorded on Thermo Fisher Scientific Q Exactive orbitrap LC-MS/MS. Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC), performed on a Shimadzu LC-20AD preparative liquid chromatograph pump system with a Shimadzu SPD-M20A UV-VIS detector set at 254 nm or Agilent 1100 series HPLC system equipped with Daicel Chemical Industries LTD. Chiralcel OD-3 column (0.46 cm x 25 cm). Reactions were followed by TLC on silica gel 60 F_{254} (E. Merck) or silicagel 70 F_{254} (Wako) using precoated TLC plates. Column chromatography was carried out on a Biotage Isolera one system using prepacked silica gel. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All solvents were of the commercially available grade. Reactions requiring anhydrous conditions were performed under nitrogen atmosphere.

Typical procedure for cyclization reaction promoted by (*S*)-TRIP (Table 1–6). (*S*)-*t*-Butyl 3-methyl-2-oxoindoline-3-carboxylate (1a): Di-*t*-butyl 2-(2-aminophenyl)-2-methylmalonate (**2a**) (63.0 mg, 0.20 mmol) was dissolved in CH_2Cl_2 (20 mL). (*S*)-TRIP (73.8 mg, 0.10 mmol) was added to the reaction mixture. The resultant mixture was stirred at room temperature for 2 h and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 90/10 – 50/50) to give 42.0 mg (87%) of (*S*)-*t*-butyl 3-methyl-2-oxoindoline-3-carboxylate (**1a**) as a colorless solid; $[\alpha]_{D}^{24}$ +61.56 (*c* 0.99, $CHCl_3$, 49% ee); mp 112–114 °C; IR (neat): 3213, 1728, 1682, 1161, 1119 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.56 (1H, br s), 7.24 (1H, t, J = 7.6 Hz), 7.18 (1H, d, J = 7.6 Hz), 6.98 (1H, t, J = 7.6 Hz), 6.87 (1H, d, J = 7.6 Hz), 1.44 (3H, s), 1.28 (9H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ:176.2, 168.5, 142.1, 131.1, 128.7, 122.6, 121.8, 109.7, 81.3, 55.7, 27.3, 19.5; HRMS (ESI): *m/z* calcd. for $C_{14}H_{17}NO_3Na$: 270.1106 [M+Na]$^+$; found: 270.1100; CSP HPLC (Chiralcel OD-3, 0.8 mL/min, 95/5 *n*-hexane/*i*-PrOH): t_R(major) = 10.10 min, t_R(minor) = 8.79 min, 49% ee.

(*S*)-*t*-Butyl 3,5-dimethyl-2-oxoindoline-3-carboxylate (1b): Yield: 92%; as a colorless solid; $[\alpha]_D^{24}$ +50.45 (*c* 1.02, $CHCl_3$, 57% ee); mp 82–83 °C; IR (neat): 3179, 1724, 1682, 1624, 1493, 1250, 1157, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.95 (1H, br s), 7.04–7.02 (2H, m), 6.77 (1H, d, *J* = 8.5 Hz), 2.32 (3H, s), 1.61 (3H, s), 1.37 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.4, 168.7, 138.2, 132.3, 131.3, 129.0, 123.8, 109.5, 82.3, 56.3, 27.7, 21.1, 19.8; HRMS (ESI): *m/z* calcd. for $C_{15}H_{19}NO_3Na$: 284.1262 $[M+Na]^+$; found: 284.1259; CSP HPLC (Chiralcel OD-3, 0.8 mL/min, 95/5 *n*-hexane/*i*-PrOH): t_R(major) = 8.07 min, t_R(minor) = 7.11 min, 57% ee.

(*S*)-*t*-Butyl 5-methoxy-3-methyl-2-oxoindoline-3-carboxylate (1c): Yield: 95%; as a colorless solid; $[\alpha]_D^{24}$ +53.92 (*c* 0.83, $CHCl_3$, 61% ee); mp 92–94 °C; IR (neat): 3217, 1728, 1678, 1489, 1250, 1203, 1157, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.96 (1H, br s), 6.84 (1H, d, *J* = 2.4 Hz), 6.82 (1H, d, *J* = 8.5 Hz), 6.77, (1H, dd, *J* = 8.5, 2.4 Hz), 3.78 (3H, s), 1.63 (3H, s), 1.37 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.2, 168.4, 156.0, 134.0, 132.5, 113.4, 110.2, 110.1, 82.4, 56.8, 55.8, 27.7, 19.9; HRMS (ESI): *m/z* calcd. for $C_{15}H_{19}NO_4Na$: 300.1212 $[M+Na]^+$; found: 300.1208; CSP HPLC (Chiralcel OD-3, 0.8 mL/min, 95/5 *n*-hexane/*i*-PrOH): t_R(major) = 11.55 min, t_R(minor) = 8.98 min, 61% ee.

(*S*)-*t*-Butyl 5-fluoro-3-methyl-2-oxoindoline-3-carboxylate (1d): Yield: 95%; as a colorless solid; $[\alpha]_D^{24}$ +52.96 (*c* 1.00, $CHCl_3$, 53% ee); mp 135–137 °C; IR (neat): 3221, 1728, 1682, 1485, 1369, 1254, 1157, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.61 (1H, br s), 6.98 (1H, dd, *J* = 10.4, 2.8 Hz), 6.95 (1H, ddd, *J* = 9.2, 8.4, 2.8 Hz), 6.86 (1H, dd, *J* = 8.4, 4.4 Hz), 1.63 (3H, s), 1.38 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.0, 167.9, 159.1 (d, *J* = 239.2 Hz), 136.9 (d, *J* = 1.9 Hz), 132.6 (d, *J* = 7.7 Hz), 115.1 (d, *J* = 23.9 Hz), 111.1 (d, *J* = 24.9 Hz), 110.8 (d, *J* = 7.7 Hz), 82.8, 57.0 (d, *J* = 1.9 Hz), 27.7, 19.9; HRMS (ESI): *m/z* calcd. for $C_{14}H_{16}FNO_3Na$: 288.1012 $[M+Na]^+$; found: 288.1006; CSP HPLC (Chiralcel OD-3, 0.8 mL/min, 95/5 *n*-hexane/*i*-PrOH): t_R(major) = 9.00 min, t_R(minor) = 7.96 min, 53% ee.

(*S*)-*t*-Butyl 3-ethyl-2-oxoindoline-3-carboxylate (1e): Yield: 95%; as a colorless solid; $[\alpha]_D^{24}$ +52.49 (*c* 0.99, $CHCl_3$, 62% ee); mp 106–109 °C; IR (neat): 3163, 1721, 1686, 1250, 1157, 1138 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, br s), 7.25–7.21 (2H, m), 7.04 (1H, t, *J* = 7.6 Hz), 6.91 (1H, d, *J* = 7.6 Hz), 2.33–2.15 (2H, m), 1.37 (9H, s), 0.71 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.9, 168.3, 141.6, 129.0, 128.6, 123.4, 122.6, 109.8, 82.2, 61.5, 27.7, 27.2, 8.1; HRMS (ESI): *m/z* calcd. for $C_{15}H_{19}NO_3Na$: 284.1262 $[M+Na]^+$; found: 284.1255; CSP HPLC (Chiralcel OD-3, 0.8 mL/min, 95/5 *n*-hexane/*i*-PrOH): t_R(major) = 8.20 min, t_R(minor) = 6.72 min, 62% ee.

(*S*)-*t*-Butyl 2-oxo-3-propylindoline-3-carboxylate (1f): Yield: 95%; as a colorless solid; $[\alpha]_D^{24}$ +56.00 (*c* 1.00, $CHCl_3$, 62% ee); mp 142–143 °C; IR (neat): 3167, 1724, 1682, 1246, 1150, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.52 (1H, br s), 7.26–7.22 (2H, m), 7.04 (1H, t, *J* = 8.0 Hz), 6.87 (1H, d, *J* = 8.0 Hz), 2.20 (1H, td, *J* = 13.2, 4.8 Hz), 2.11 (1H, td, *J* = 13.2, 4.8 Hz), 1.37 (9H, s), 1.20–1.11 (1H, m), 1.04–0.94 (1H, m), 0.85 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.2, 168.3, 141.5, 129.3, 128.6, 123.4, 122.5, 109.9, 82.3, 61.0, 36.1, 27.7, 17.1, 14.1; HRMS (ESI): *m/z* calcd. for $C_{16}H_{21}NO_3Na$: 298.1419 [M+Na]$^+$; found: 298.1411; CSP HPLC (Chiralcel OD-3, 0.8 mL/min, 95/5 *n*-hexane/*i*-PrOH): t_R(major) = 7.03 min, t_R(minor) = 6.18 min, 62% ee.

(*S*)-*t*-Butyl 3-benzyl-2-oxoindoline-3-carboxylate (1g)[4a]**:** Yield: 92%; as a colorless solid; $[\alpha]_D^{24}$ +97.96 (*c* 0.98, $CHCl_3$, 60% ee) [Lit.[4b] (*R*)-**1g**, $[\alpha]_D^{25}$ −148.4 (*c* 0.5, $CHCl_3$, 95% ee)]; mp 167–169 °C; IR (neat): 3179, 1724, 1682, 1470, 1254, 1150, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (1H, br s), 7.31 (1H, d, *J* = 7.7 Hz), 7.16 (1H, t, *J* = 7.7 Hz), 7.06–7.00 (4H, m), 6.90 (2H, d, *J* = 6.6 Hz), 6.66 (1H, d, *J* = 7.7 Hz), 3.51 (2H, s), 1.39 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.7, 167.9, 141.2, 134.7, 130.0, 128.8, 128.4, 127.7, 126.7, 124.0, 122.3, 109.7, 82.6, 62.1, 39.4, 27.7; HRMS (ESI): *m/z* calcd. for $C_{20}H_{21}NO_3Na$: 346.1419 [M+Na]$^+$; found: 346.1410; CSP HPLC (Chiralcel OD-3, 0.8 mL/min, 95/5 *n*-hexane/*i*-PrOH): t_R(major) = 11.66 min, t_R(minor) = 7.35 min, 60% ee.

(*S*)-*t*-Butyl 5-methoxy-2-oxo-3-propylindoline-3-carboxylate (1h)[4b]**:** Yield: 97%; as a colorless solid; $[\alpha]_D^{24}$ +29.55 (*c* 1.00, $CHCl_3$, 66% ee) [Lit.[4b] (*S*)-**1h**, $[\alpha]_D^{20}$ +44.31 (*c* 1, $CHCl_3$, 83% ee)]; mp 140–144 °C; IR (neat): 3271, 1724, 1678, 1493, 1250, 1204, 1153 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (1H, br s), 6.83 (1H, d, *J* = 2.4 Hz), 6.82 (1H, d, *J* = 8.5 Hz), 6.76 (1H, dd, *J* = 8.5, 2.4 Hz), 3.78 (3H, s), 2.20 (1H, ddd, *J* = 13.6, 12.0, 4.8 Hz), 2.09 (1H, ddd, *J* = 13.6, 12.0, 4.8 Hz), 1.37 (9H, s), 1.21–1.09 (1H, m), 1.05–0.94 (1H, m), 0.84 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.8, 168.2, 155.8, 134.8, 130.7, 113.2, 110.5, 110.1, 82.3, 61.4, 55.8, 36.2, 27.7, 17.1, 14.1; HRMS (ESI): *m/z* calcd. for $C_{17}H_{23}NO_4Na$: 328.1525 [M+Na]$^+$; found: 328.1521; CSP HPLC (Chiralcel OD-3, 0.8 mL/min, 95/5 *n*-hexane/*i*-PrOH): t_R(major) = 8.08 min, t_R(minor) = 7.33 min, 66% ee.

Typical procedure for malonate derivatives. Di-*t*-butyl 2-(5-methyl-2-nitrophenyl)malonate (8b): To a solution of di-*t*-butyl malonate (7.57 mL, 33.8 mmol) in DMF (40 mL) was added NaH (55% in mineral oil, 2.84 g, 70.9 mmol) at 0 °C. After 10 min, a solution of 2-fluoro-4-methylnitrobenzene (5.00 g, 32.2 mmol) in DMF (6 mL) was added dropwise. The resultant mixture was stirred at room temperature for 23 h. The reaction mixture was diluted with 0.5N HCl aq. (500 mL) and extracted with EtOAc/*n*-hexane = 2/1 (500 mL). The organic phase was washed with 0.1N HCl aq. (500 mL), dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. The residue was triturated with *n*-hexane to give 3.40 g (31%) of di-*t*-butyl 2-(5-methyl-2-nitrophenyl)malonate (**8b**) as a colorless solid. mp 114–116 °C; IR (neat): 1724, 1520, 1335, 1250, 1161, 1138 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.02 (1H, d, *J* = 8.3 Hz), 7.43 (1H, d, *J* = 8.3 Hz), 7.25 (1H, s), 5.08 (1H, s), 2.42 (3H, s), 1.43 (18H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.8, 146.2, 144.6, 131.5, 129.7, 128.7, 125.2, 82.1, 56.4, 27.4, 20.9; HRMS (ESI): *m/z* calcd. for $C_{18}H_{25}NO_6Na$: 374.1580 [M+Na]$^+$; found: 374.1575.

Typical procedure for alkylation reaction of malonate derivatives. Di-*t*-butyl 2-methyl-2-(5-methyl-2-nitrophenyl)malonate (9b): Di-*t*-butyl 2-(5-methyl-2-nitrophenyl)malonate (**8b**) (1.70 g, 4.84 mmol) was dissolved in DMF (7 mL). K_2CO_3 (869 mg, 6.29 mmol) and iodomethane (361 μL, 5.81 mmol) were added to the reaction mixture. The resultant mixture was stirred at room temperature for 13 h. The reaction mixture was diluted with water (150 mL) and extracted with EtOAc/*n*-hexane = 2/1 (300 mL). The organic phase was washed with water, dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 100/0 – 90/10) to give 1.40 g (79%) of di-*t*-butyl 2-methyl-2-(5-methyl-2-nitrophenyl)malonate (**9b**) as a yellow solid. mp 86–87 °C; IR (neat): 1728, 1524, 1346, 1145, 1115 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.94 (1H, d, *J* = 8.3 Hz), 7.38 (1H, dd, *J* = 8.3, 0.7 Hz), 7.03 (1H, d, *J* = 0.7 Hz), 2.39 (3H, s), 1.80 (3H, s), 1.37 (18H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 167.8, 146.2, 144.2, 134.6, 129.6, 129.0, 125.7, 82.2, 60.4, 27.1, 23.6, 20.9; HRMS (ESI): *m/z* calcd. for $C_{19}H_{27}NO_6Na$: 388.1736 $[M+Na]^+$; found: 388.1730.

Typical procedure for allylation reaction of malonate derivatives. Di-*t*-butyl 2-(2-nitrophenyl)-2-(prop-2-en-1-yl)malonate (9f): Di-*t*-butyl 2-(2-nitrophenyl)malonate (**8**) (330 mg, 0.98 mmol) was dissolved in DMF (3 mL). K_2CO_3 (406 mg, 2.9 mmol) and allyl bromide (235 mg, 2.0 mmol) were added to the reaction mixture. The resultant mixture was stirred at room temperature for 8 h. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc/*n*-hexane = 1/1 (30 mL). The organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 100/0 – 80/20) to give 324 mg (88%) of di-*t*-butyl 2-(2-nitrophenyl)-2-(prop-2-en-1-yl)malonate (**9f**) as a white solid. mp 67–69 °C; IR (neat): 1736, 1524, 1354, 1281, 1138, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.97 (1H, dd, *J* = 7.8, 1.3 Hz), 7.53 (1H, td, *J* = 7.8, 1.3 Hz), 7.42 (1H, td, *J* = 7.8, 1.3 Hz), 7.27 (1H, dd, *J* = 7.8, 1.3 Hz), 5.78–5.68 (1H, m), 4.98 (1H, dq, *J* = 17.0, 1.3 Hz), 4.94–4.91 (1H, m), 3.25 (2H, dt, *J* = 7.2, 1.3 Hz), 1.44 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ:167.9, 149.6, 133.8, 132.9, 132.0, 131.2, 128.0, 125.5, 118.5, 82.9, 64.4, 39.7, 27.6; HRMS (ESI): *m/z* calcd. for $C_{20}H_{27}NO_6Na$: 400.1736 $[M+Na]^+$; found: 400.1734.

Di-*t*-butyl 2-(5-methoxy-2-nitrophenyl)-2-(prop-2-en-1-yl)malonate (9h): Yield: 95%; as a yellow oil; IR (neat): 1728, 1578, 1520, 1346, 1246, 1138 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.09 (1H, d, *J* = 9.0 Hz), 6.85 (1H, dd, *J* = 9.0, 2.7 Hz), 6.81 (1H, d. *J* = 2.7 Hz), 5.77 (1H, ddt, *J* = 17.1, 10.2, 6.8 Hz), 5.03 (1H, d, *J* = 17.1 Hz), 4.96 (1H, d, *J* = 10.2 Hz), 3.86 (3H, s), 3.23 (2H, d, *J* = 6.8 Hz), 1.44 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 162.4, 142.5, 135.9, 133.9, 128.2, 118.4, 117.4, 111.4, 82.8, 64.4, 55.7, 39.6, 27.7; HRMS (ESI): *m/z* calcd. for $C_{21}H_{29}NO_7Na$: 430.1842 $[M+Na]^+$; found: 430.1831.

Di-*t*-butyl 2-benzyl-2-(2-nitrophenyl)malonate (9g): Di-*t*-butyl 2-(2-nitrophenyl)malonate (**8**) (1.00 g, 2.96 mmol) was dissolved in DMF (10 mL). K_2CO_3 (901 mg, 6.52 mmol) and benzyl bromide (705 μL, 5.94 mmol) were added to the reaction mixture. The resultant mixture was stirred at room temperature for 14 h. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (80 mL). The organic phase was washed with water (100 mL), dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo* to give 1.00 g (79%) of di-*t*-butyl 2-benzyl-2-(2-nitrophenyl)malonate (**9g**) as a colorless solid. mp 99–100 °C; IR (neat): 1728, 1531, 1358, 1254, 1138, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.88 (1H, d, J = 7.8 Hz), 7.28 (1H, t, J = 7.8 Hz), 7.14 (1H, t, J = 7.8 Hz), 7.03–7.00 (5H, m), 6.52 (1H, d, J = 7.8 Hz), 3.91 (2H, s), 1.44 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 149.8, 137.4, 132.5, 132.4, 131.1, 130.9, 127.7, 127.4, 126.1, 124.9, 83.2, 66.8, 40.2, 27.6; HRMS (ESI): *m/z* calcd. for $C_{24}H_{29}NO_6Na$: 450.1893 $[M+Na]^+$; found: 450.1884.

Typical procedure for catalytic hydrogenation. Di-*t*-butyl 2-(2-amino-5-methylphenyl)-2-methylmalonate (2b): Di-*t*-butyl 2-methyl-2-(5-methyl-2-nitrophenyl)malonate (**9b**) (300 mg, 0.82 mmol) was dissolved in MeOH (16 mL). 10% Pd/C (175 mg) were added to the reaction mixture. The resultant mixture was stirred at 0 °C under H_2 atmosphere. After 4 h, the mixture was passed through a pad of Celite with MeOH and the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 80/20) to give 270 mg (98%) of di-*t*-butyl 2-(2-amino-5-methylphenyl)-2-methylmalonate (**2b**) as a colorless solid. mp 102–104 °C; IR (neat): 3433, 3364, 1732, 1705, 1508, 1366, 1261, 1161, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.92 (1H, s), 6.89 (1H, d, J = 8.0 Hz), 6.61 (1H, d, J = 8.0 Hz), 4.00 (2H, s), 2.23 (3H, s), 1.80 (3H, s), 1.48 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.2, 143.1, 128.8, 127.8, 127.7, 125.9, 118.7, 81.8, 59.0, 27.8, 22.0, 20.7; HRMS (ESI): *m/z* calcd. for $C_{19}H_{30}NO_4$: 336.2175 $[M+H]^+$; found: 336.2168.

Di-*t*-butyl 2-(2-amino-5-methoxyphenyl)-2-methylmalonate (2c): Yield: 79%; as a colorless solid; mp 109–110 °C; IR (neat): 3433, 3364, 1728, 1705, 1504, 1369, 1258, 1161, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.75 (1H, d, J = 2.4 Hz), 6.68 (1H, dd, J = 8.5, 2.4 Hz), 6.65 (1H, d, J = 8.5 Hz), 3.85 (2H, s), 3.74 (3H, s), 1.80 (3H, s), 1.47 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.0, 152.8, 139.3, 127.9, 119.7, 114.1, 113.1, 81.9, 59.2, 55.7, 27.8, 22.0; HRMS (ESI): *m/z* calcd. for $C_{19}H_{30}NO_5$: 352.2124 $[M+H]^+$; found: 352.2119.

Di-*t*-butyl 2-(2-amino-5-fluorophenyl)-2-methylmalonate (2d): Yield: 94%; as a colorless solid; mp 86–87 °C; IR (neat): 3426, 3345, 1728, 1713, 1501, 1366, 1277, 1161, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.90 (1H, dd, J = 10.7, 2.7 Hz), 6.80 (1H, td, J = 8.5, 2.7 Hz), 6.63 (1H, dd. J = 8.5, 5.1 Hz), 4.05 (2H, s), 1.79 (3H, s), 1.47 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.7, 156.3 (d, J = 235.0 Hz), 141.9 (d, J = 1.7 Hz), 127.4 (d, J = 6.5 Hz), 119.3 (d, J = 7.4 Hz), 114.7 (d, J = 22.2 Hz), 114.1 (d, J = 23.9 Hz), 82.2, 58.8, 27.8, 22.1; HRMS (ESI): *m/z* calcd. for $C_{18}H_{27}FNO_4$: 340.1924 $[M+H]^+$; found: 390.1922.

Di-*t*-butyl 2-(2-aminophenyl)-2-ethylmalonate (2e): Yield: 93%; as a colorless solid; mp 92–94 °C; IR (neat): 3429, 3364, 1728, 1705, 1454, 1369, 1250, 1157, 1126 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.18 (1H, d, *J* = 7.8 Hz), 7.06 (1H, t, *J* = 7.8 Hz), 6.74 (1H, t, *J* = 7.8 Hz), 6.66 (1H, d, *J* = 7.8 Hz), 4.26 (2H, s), 2.34 (2H, q, *J* = 7.2 Hz), 1.44 (18H, s), 0.99 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 170.0, 146.0, 128.1, 127.6, 124.5, 118.3, 118.1, 81.8, 62.5, 27.9, 27.9, 9.9; HRMS (ESI): *m/z* calcd. for $C_{19}H_{30}NO_4$: 336.2175 [M+H]$^+$; found: 336.2168.

Di-*t*-butyl 2-(2-aminophenyl)-2-propylmalonate (2f): Yield: 97%; as a colorless solid; mp 91–92 °C; IR (neat): 3433, 3360, 1724, 1705, 1454, 1366, 1238, 1161, 1130 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.17 (1H, d, *J* = 7.6 Hz), 7.06 (1H, t, *J* = 7.6 Hz), 6.74 (1H, t, *J* = 7.6 Hz), 6.66 (1H, d, *J* = 7.6 Hz), 4.27 (2H, s), 2.25–2.21 (2H, m), 1.44 (18H, s), 1.41–1.28 (2H, m), 0.98 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 170.1, 145.9, 128.1, 127.5, 124.7, 118.3, 118.1, 81.8, 62.1, 37.1, 27.8, 18.8, 14.7; HRMS (ESI): *m/z* calcd. for $C_{20}H_{32}NO_4$: 350.2331 [M+H]$^+$; found: 350.2325.

Di-*t*-butyl 2-(2-aminophenyl)-2-benzylmalonate (2g): Yield: 86%; as a colorless oil; IR (neat): 3444, 3372, 1717, 1454, 1366, 1250, 1142 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.24–7.16 (6H, m), 7.08 (1H, t, *J* = 7.8 Hz), 6.72 (1H, t, *J* = 7.8 Hz), 6.67 (1H, d, *J* = 7.8 Hz), 4.12 (2H, s), 3.70 (2H, s), 1.35 (18H, s); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 169.3, 145.4, 137.3, 130.7, 128.3, 128.2, 127.6, 126.4, 124.7, 118.5, 118.4, 82.1, 63.6, 40.4, 27.7; HRMS (ESI): *m/z* calcd. for $C_{24}H_{32}NO_4$: 398.2331 [M+H]$^+$; found: 398.2323.

Di-*t*-butyl 2-(2-amino-5-methoxyphenyl)-2-propylmalonate (2h): Yield: 79%; as a colorless oil; IR (neat): 3429, 3364, 1717, 1501, 1369, 1231, 1161, 1119 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 6.79 (1H, d, *J* = 2.7 Hz), 6.67 (1H, dd, *J* = 8.5, 2.7 Hz), 6.61 (1H, d. *J* = 8.5 Hz), 3.92 (2H, s), 3.74 (3H, s), 2.24–2.20 (2H, m), 1.45 (18H, s), 1.39–1.33 (2H, m), 0.97 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 170.0, 152.6, 139.2, 126.8, 119.4, 114.6, 113.0, 81.9, 62.4, 55.7, 37.0, 27.8, 18.8, 14.7; HRMS (ESI): *m/z* calcd. for $C_{21}H_{34}NO_5$: 380.2437 [M+H]$^+$; found: 380.2433.

ACKNOWLEDGEMENTS

Part of this work was supported by the Kansai University Subsidy for Supporting Young Scholars, 2015 “Development of macrocyclization reaction via a photoaffinity reaction”, JSPS KAKENHI Grant Number 15K18903, Grant-in-Aid for Young Scientists (B) – Japan and MEXT – Supported Program for the Strategic Research Foundation at Private Universities (2013–2017) – Japan.

REFERENCES

1. a) A. Ashimori, T. Matsuura, L. E. Overman, and D. J. Poon, *J. Org. Chem.*, 1993, **58**, 6949; b) M. Pallavicini, E. Valoti, L. Villa, and I. Resta, *Tetrahedron: Asymmetry*, 1994, **5**, 363; c) B. M. Trost

and J. Quancard, *J. Am. Chem. Soc.*, 2006, **128**, 6314; d) T. Kawasaki, M. Shinada, M. Ohzono, A. Ogawa, R. Terashima, and M. Sakamoto, *J. Org. Chem.*, 2008, **73**, 5959; e) Y. Zhou, Y. Xi, J. Zhao, X. Sheng, S. Zhang, and H. Zhang, *Org. Lett.*, 2012, **14**, 3116; f) S. De, M. K. Das, S. Bhunia, and A. Bisai, *Org. Lett.*, 2015, **17**, 5922; g) S. Ghosh, S. Chaudhuri, and A. Bisai, *Chem. Eur. J.*, 2015, **21**, 17479; h) M. Shinada, F. Narumi, Y. Osada, K. Matsumoto, T. Yoshida, K. Higuchi, T. Kawasaki, H. Tanaka, and M. Satoh, *Bioorg. Med. Chem.*, 2012, **20**, 4901.

2. a) C. Uyeda, A. R. Rötheli, and E. N. Jacobsen, *Angew. Chem. Int. Ed.*, 2010, **49**, 9753; b) B. M. Trost and M. K. Brennan, *Org. Lett.*, 2006, **8**, 2027; c) X. Chen, W. Zhu, W. Qian, E. Feng, Y. Zhou, J. Wang, H. Jiang, Z.-J. Yao, and H. Liu, *Adv. Synth. Catal.*, 2012, **354**, 2151; d) J. Gao, J.-R. Chen, S.-W. Duan, T.-R. Li, L.-Q. Lu, and W.-J. Xiao, *Asian J. Org. Chem.*, 2014, **3**, 530; e) Z.-W. Lai, C. Liu, H. Sun, and S.-L. You, *Chin. J. Chem.*, 2017, **35**, 1512; f) J. Zhou, L.-N. Jia, L. Peng, Q.-L. Wang, F. Tian, X.-Y. Xu, and L.-X. Wang, *Tetrahedron*, 2014, **70**, 3478; g) I. D. Hills and G. C. Fu, *Angew. Chem. Int. Ed.*, 2003, **42**, 3921; h) S. A. Shaw, P. Aleman, and E. Vedejs, *J. Am. Chem. Soc.*, 2003, **125**, 13368; i) S. A. Shaw, P. Aleman, J. Christy, J. W. Kampf, P. Va, and E. Vedejs, *J. Am. Chem. Soc.*, 2006, **128**, 925; j) T. A. Duffey, S. A. Shaw, and E. Vedejs, *J. Am. Chem. Soc.*, 2009, **131**, 14; k) M. Ismail, H. V. Nguyen, G. Ilyashenko, M. Motevalli, and C. J. Richards, *Tetrahedron Lett.*, 2009, **50**, 6332.
3. a) E. C. Linton and M. C. Kozlowski, *J. Am. Chem. Soc.*, 2008, **130**, 16162; b) T. Cao, E. C. Linton, J. Deitch, S. Berritt, and M. C. Kozlowski, *J. Org. Chem.*, 2012, **77**, 11034.
4. a) S. Hong, J. Lee, M. Kim, Y. Park, C. Park, M.-h. Kim, S.-s. Jew, and H.-g. Park, *J. Am. Chem. Soc.*, 2011, **133**, 4924; b) S. Hong, M. Jung, Y. Park, M. W. Ha, C. Park, M. Lee, and H.-g. Park, *Chem. Eur. J.*, 2013, **19**, 9599.
5. a) R. M. Acheson, R. J. Prince, and G. Procter, *J. Chem. Soc., Perkin Trans. 1*, 1979, 595; b) B. Nammalwar, R. A. Bunce, and J. T. Hiett, *Org. Prep. Proced. Int.*, 2015, **47**, 338.
6. Y. Yamai, A. Tanaka, T. Yajima, K. Ishida, I. Natsutani, S. Uesato, Y. Nagaoka, and T. Sumiyoshi, *Heterocycles*, 2018, **97**, 192.
7. a) G. Qabaja, J. E. Wilent, A. R. Benavides, G. E. Bullard, and K. S. Petersen, *Org. Lett.*, 2013, **15**, 1266; b) J. Wilent and K. S. Petersen, *J. Org. Chem.*, 2014, **79**, 2303.
8. V. Martì-Centelles, M. D. Pandey, M. I. Burguete, and S. V. Luis, *Chem. Rev.*, 2015, **115**, 8736.
9. H.-J. Knölker, M. Graf, and U. Mangei, *J. Prakt. Chem.*, 1998, **340**, 530.
10. J. W. Hulshof, H. F. Vischer, M. H. P. Verheij, S. A. Fratantoni, M. J. Smit, I. J. P. de Esch, and R. Leurs, *Bioorg. Med. Chem.*, 2006, **14**, 7213.