Organic & Biomolecular Chemistry

Accepted Manuscript

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ARTICLE

Enantioselective organocatalyzed aza-Morita–Baylis–Hillman reaction of isatin-derived ketimines with acrolein

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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A highly enantioselective aza-Morita–Baylis–Hillman (aza-MBH) reaction of isatin-derived ketimines with acrolein was established using β-isocupreidine (β-ICD) or α-isocupreine (α-ICPN) as a chiral acid-base organocatalyst. The present protocol readily furnished (*S*) or (*R*)-aza-MBH adducts with a chiral tetrasubstituted carbon stereogenic center in up to 98% ee.

Introduction

Chiral 3-amino-2-oxindoles are important structural motifs found in various biologically active compounds such as nelivaptan (SSR-149,415), an orally active non-peptide vasopressin receptor antagonist, and AG-041R, a gastrin/cholecystokinin-B receptor antagonist (Figure 1).[1] To date, considerable efforts have been devoted to the development of efficient strategies to synthesize chiral 3-amino-2-oxindoles.[2] Among them, the enantioselective aza-Morita–Baylis–Hillman (aza-MBH) reaction[3] of isatin-derived ketimines gives highly functionalized 3-amino-2-oxindoles having a chiral tetrasubstituted carbon stereogenic center.[4-7] In 2013, Shi and Li reported the aza-MBH reaction of *N*-*tert*-butoxycarbonyl (Boc) protected ketimines **1** with methyl vinyl ketone using chiral acid-base organocatalysts.[4] Sha and Wu also discovered that chiral phosphine-squaramide promoted the aza-MBH reaction of acrylates with 1-Me protected isatin-derived ketimines.[5] In 2015, Chimni found that maleimides were appropriate nucleophilic partners for the aza-MBH process.[6] However the efficient enantioselective construction of 3-amino-2-oxindoles possessing a tetrasubstituted carbon stereogenic center *via* the aza-MBH reaction has been a challenge in catalytic asymmetric synthesis. Herein, we report enantiodiscriminating aza-MBH processes of isatin-derived ketimines **1** with acrolein (**2**) using β-isocupreidine (β-ICD)[8a-c] or α-isocupreine (α-ICPN)[8d] as natural alkaloid-derived chiral acid-base organocatalysts (Scheme 1). The present protocol with β-ICD or α-ICPN selectively gave (*S*) or (*R*)-adduct **3** in up to 98% ee.

Results and discussion

First, we studied the effect of solvent and temperature on the reaction of isatin-derived ketimine **1a** with **2** (Table 1).

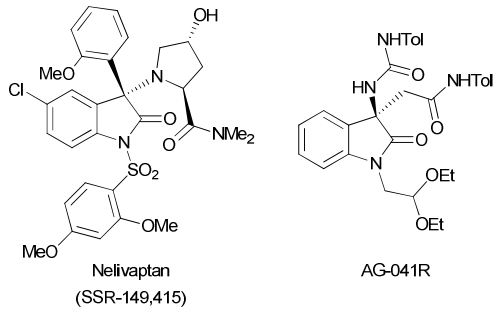
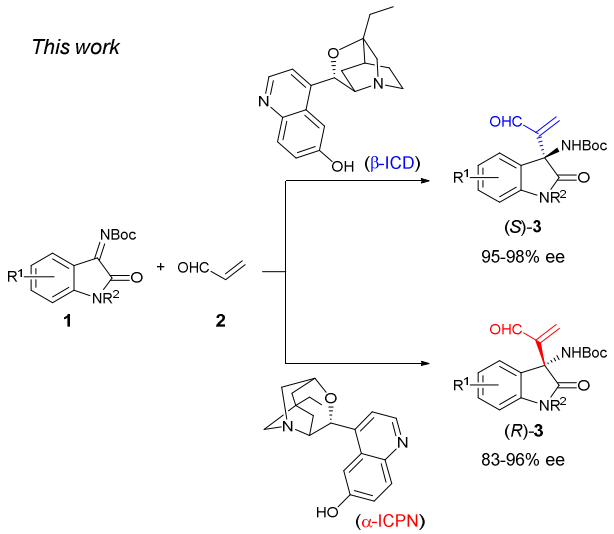


Fig. 1 Bioactive products with a 3-amino-2-oxindole skeleton.

Scheme 1 Enantioselective organocatalyzed aza-MBH reaction of isatin-derived ketimines **1** with **2**.



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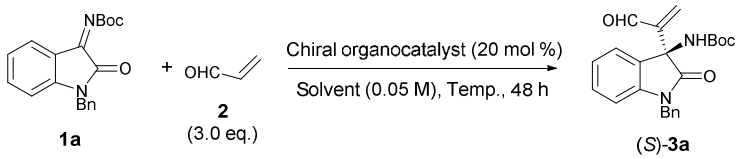
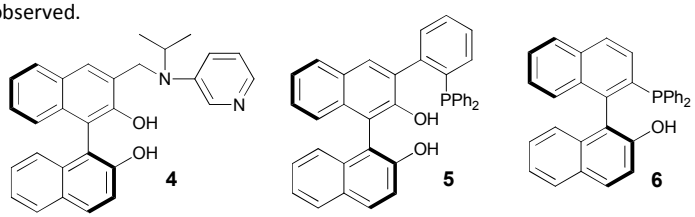
Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x

Table 1 Optimization of the reaction conditions.[a]



Entry	Solvent	Chiral organocatalyst	Temp. (°C)	Yield (%)[b]	ee (%)[c]
1	toluene	β-ICD	-15	54	89
2	CH_2Cl_2	β-ICD	-15	51	64
3	THF	β-ICD	-15	62	80
4	CPME[d]	β-ICD	-15	58	87
5	toluene	β-ICD	10[e]	27	93
6	toluene	β-ICD	-10	65	88
7	toluene	β-ICD	-20	53	90
8	toluene	β-ICD	-40	46	94
9	toluene	β-ICD	-60	19	97
10	toluene/CPME = 1/1	β-ICD	-40	60	94
11	toluene/CPME = 1/1	**4**	-40	Trace	-
12	toluene/CPME = 1/1	**5**	-40	16	90
13	toluene/CPME = 1/1	**6**	-40	35	80

[a] **1a** (0.06 mmol) in the stated solvent (0.05 M for **1a**), chiral organocatalyst (0.012 mmol) and **2** (0.18 mmol) were stirred for 48 h.
[b] ^{1}H-NMR yield of product **3a** using 1,3,5-trimethoxybenzene as an internal standard.
[c] Determined by HPLC (Daicel Chiralpak IE).
[d] Cyclopentyl methyl ether (CPME).
[e] Over reaction of **3a** with **2** was observed.



During the initial solvent screening (-15 °C, 20 mol % β-ICD), we found that the reaction proceeded better in toluene or cyclopentyl methyl ether (CPME) than in other solvents such as CH_2Cl_2 and THF (entries 1–4). Next we investigated the effect of the reaction temperature. Decreasing the reaction temperature to -40 °C gave **3a** in an acceptable yield (46%) with 94% ee (entry 8). When the reaction was performed at 10 °C or -60 °C, **3a** was obtained in low yields because of either over reaction of **3a** with **2** (involving polymerization of **2**)[9] (entry 5) or low conversion (entry 9), respectively. Finally, we discovered that the use of mixed-solvent system toluene/CPME (1/1) for the aza-MBH reaction of **1a** with **2** at -40 °C gave **3a** in 60% yield with 94% ee (entry 10). Chiral acid-base organocatalysts **4**–**6**, which are known to mediate enantioselective aza-MBH processes,[10] were virtually ineffective at improving the chemical yields and ee values for **3a** (entries 11–13).

The optimal result (**3a**: 81% yield, 97% ee) was obtained when the reaction of **1a** and **2** (2.0 eq.) was performed with β-ICD (15 mol %) in toluene/CPME (1/1; 0.05 M with respect to **1**) at -40 °C in the presence of 3Å molecular sieves (MS3A) as an additive (Table 2, entry 1). *N*-Substituted ketimines **1b**–**1d** (R^1 = allyl, Ph, prenyl) were transformed to **3b**–**3d** in 48–70% yields with excellent enantioselectivities (95–98% ee) (entries 3–5). Ketimines **1e**–**1j** bearing an electron-withdrawing or electron-donating substituent on the aromatic ring also afforded the corresponding aza-MBH adducts **3e**–**3j** in 68–83% yields with excellent enantioselectivities (95–98% ee) (entries 6–11). The absolute configuration of **3k** was assigned as *S* by comparison with the optical rotation and HPLC data of allyl alcohol **7a** derived from known compound **3l** (Scheme 2).[5] The aza-MBH product **3a** was also able to be converted into allyl alcohol derivatives **7b** and **9** (Scheme 3).

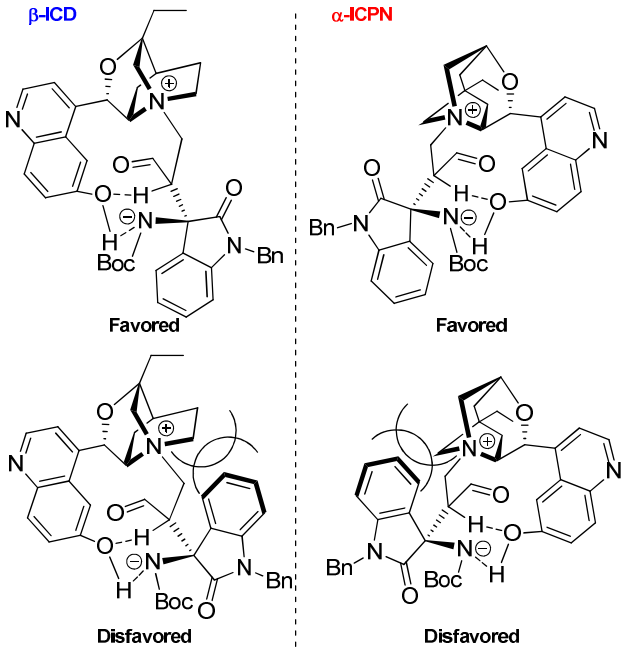
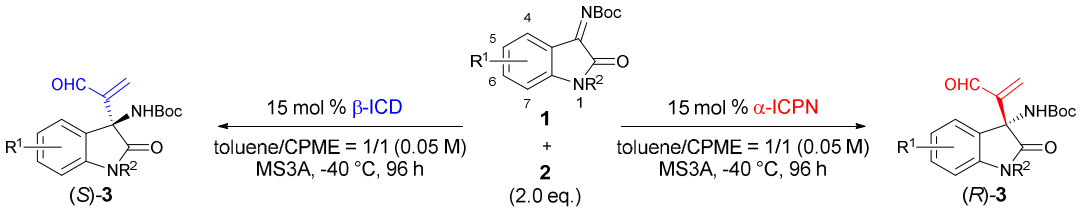


Fig. 2 Plausible model of enantioselection.

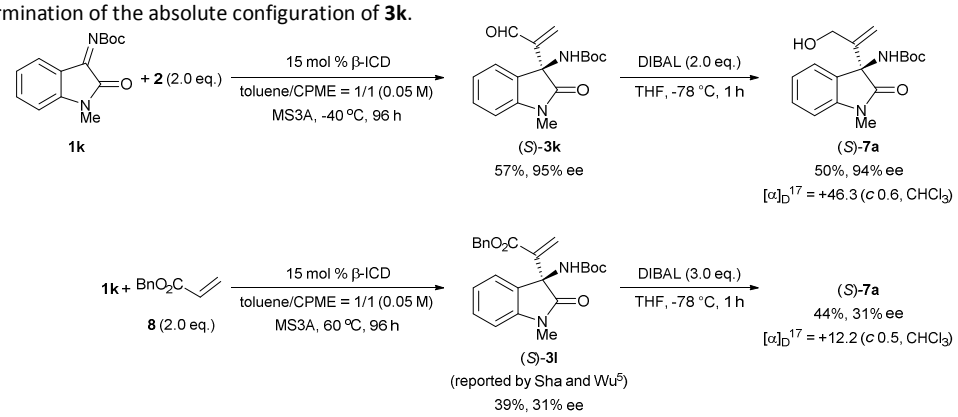
Table 2 Substrate scope in the aza-MBH reaction catalyzed by β-ICD or α-ICPN.[a]



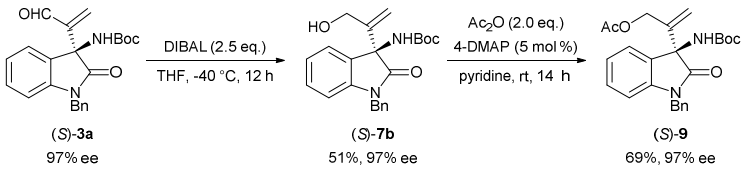
Entry	β-ICD or α-ICPN	1	Yield (%)[b]	ee (%)[c]
1	β-ICD	**1a**, R^1 = H, R^2 = Bn	**3a**, 81	97 (***S***)
2[d]	β-ICD	**1a**	**3a**, 76	97 (***S***)
3	β-ICD	**1b**, R^1 = H, R^2 = allyl	**3b**, 70	96 (***S***)
4	β-ICD	**1c**, R^1 = H, R^2 = Ph	**3c**, 52	98 (***S***)
5	β-ICD	**1d**, R^1 = H, R^2 = prenyl	**3d**, 48	95 (***S***)
6	β-ICD	**1e**, R^1 = 5-Cl, R^2 = Bn	**3e**, 68	98 (***S***)
7	β-ICD	**1f**, R^1 = 6-Cl, R^2 = Bn	**3f**, 83	98 (***S***)
8	β-ICD	**1g**, R^1 = 7-Cl, R^2 = Bn	**3g**, 81	97 (***S***)
9	β-ICD	**1h**, R^1 = 5-Br, R^2 = Bn	**3h**, 73	96 (***S***)
10	β-ICD	**1i**, R^1 = 5-F, R^2 = Bn	**3i**, 78	98 (***S***)
11[e]	β-ICD	**1j**, R^1 = 5-Me, R^2 = Bn	**3j**, 77	95 (***S***)
12	α-ICPN	**1a**, R^1 = H, R^2 = Bn	**3a**, 78	95 (***R***)
13	α-ICPN	**1b**, R^1 = H, R^2 = allyl	**3b**, 59	90 (***R***)
14	α-ICPN	**1c**, R^1 = H, R^2 = Ph	**3c**, 37	87 (***R***)
15	α-ICPN	**1d**, R^1 = H, R^2 = prenyl	**3d**, 44	89 (***R***)
16	α-ICPN	**1e**, R^1 = 5-Cl, R^2 = Bn	**3e**, 74	87 (***R***)
17	α-ICPN	**1g**, R^1 = 7-Cl, R^2 = Bn	**3g**, 44	94 (***R***)
18	α-ICPN	**1h**, R^1 = 5-Br, R^2 = Bn	**3h**, 79	88 (***R***)
19[f]	α-ICPN	**1j**, R^1 = 5-Me, R^2 = Bn	**3j**, 58	96 (***R***)
20	α-ICPN	**1k**, R^1 = H, R^2 = Me	**3k**, 45	83 (***R***)
21	β-ICD or α-ICPN	**1m**, R^1 = 4-Cl, R^2 = Bn	**3m**, Trace	-
22	β-ICD or α-ICPN	**1n**, R^1 = R^2 = H	**3n**, Trace	-

[a] **1** (0.06 mmol) in toluene/CPME (1/1, 0.05 $_M$ for **1**), β-ICD or α-ICPN (0.009 mmol) and **2** (0.12 mmol) were stirred for 96 h at -40 °C, unless otherwise noted.
[b] Isolated product yield.
[c] Determined by HPLC (Daicel Chiralpak IE). Configuration of the major isomer is shown in parentheses.
[d] 0.64 mmol of **1a** was used.
[e] β-ICD (25 mol %), -20 °C.
[f] α-ICPN (25 mol %).

Scheme 2 Determination of the absolute configuration of **3k**.



Scheme 3 Transformation of the aza-MBH adduct **3a**.



Although the β-ICD-mediated aza-MBH process exhibited high asymmetric induction, the present system is difficult to apply to the synthesis of (*R*)-**3** because the required enantiomer of β-ICD is not readily available. One solution to this problem was the use of α-ICPN, derived from quinine, as an effective enantiocomplementary catalyst of β-ICD, which gave the corresponding aza-MBH adducts (*R*)-**3** in 37−79% yields with high enantioselectivities (83−96% ee) (entries 12−20). Although the reaction of **1j** with **2** required a higher catalyst loading (25 mol %) due to the low reactivity of **1j** (entries 11 and 19), the reaction of **1m** and **1n** gave no product because of quite low reactivity of **1m** and instability of **1n** (entries 21 and 22). A proposed model for the enantioselectivity is shown in Figure 2. Since proton transfer is a known rate-determining step in aza-MBH reactions,[11] the proton shift mediated by the acidic unit on the catalyst could proceed smoothly *via* an intermediate conformation with the least steric hindrance between the quinuclidine moiety of the catalyst and the aromatic ring of the substrate to result in the formation of (*S*)-**3** with β-ICD or (*R*)-**3** with α-ICPN.

Conclusions

We have developed a highly enantioselective organocatalyzed aza-MBH reaction of isatin-derived ketimines **1** with **2**. Aza-MBH adducts **3** were obtained in excellent enantioselectivities (up to 98% ee), irrespective of the electronic nature of the ketimine moiety. Moreover, both enantiomers of aza-MBH adducts **3** with a chiral tetrasubstituted carbon stereogenic center were successfully obtained by using either β-ICD or α-ICPN.

Experimental section

General procedure for enantioselective organocatalyzed aza-MBH reaction of isatin-derived ketimines 1 with acrolein (2) or benzyl acrylate (8): A test tube was filled with *N*-Boc protected ketimines **1** (0.060 mmol), β-ICD or α-ICPN (0.009 mmol) and MS3A (20 mg) in toluene/CPME (1/1, 1.2 mL). Then, **2** or **8** (0.12 mmol) was added under -40 °C (for **2**) or 60 °C (for **8**). After 96 h, reaction mixture was filtered quickly with silica gel, washed with ethyl acetate and dried in *vacuo*. Resulting crude product was purified by silica gel column chromatography using hexane/ethyl acetate as eluent, and followed by GPC using chloroform as eluent to give product **3** as white solid or colorless oil.

3a; 81% yield (19.1 mg) with β-ICD, 78% yield (18.4 mg) with α-ICPN; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H) 7.60-7.26 (m, 6H), 7.18 (td, 1H, *J* = 7.8, 0.8 Hz), 7.00 (td, 1H, *J* = 7.8, 0.8 Hz), 6.72 (d, 1H, *J* = 7.8 Hz), 6.44 (s, 1H), 6.23 (s, 1H), 6.05 (s, 1H), 5.15 (d, 1H, *J* = 15.6 Hz), 4.86 (d, 1H, *J* = 15.6 Hz), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 174.3, 154.0, 145.4, 142.7, 137.2, 135.6, 129.3, 129.0, 128.8, 127.6, 127.3, 124.8, 123.0, 109.4, 80.6, 63.4, 44.4, 28.1; HRMS (ESI) calcd for $C_{23}H_{24}N_2O_4Na^+$ 415.1628, found 415.1624; IR (KBr) *v* 3329, 2972, 1712, 1612, 1487, 1366, 1167, 1004, 758 cm^{-1}; $[\alpha]_D^{22}$ = -132.7 (*c* 0.4, $CHCl_3$) for (*S*)-**3a** in 97% ee; $[\alpha]_D^{17}$ = +130.1 (*c* 0.4, $CHCl_3$) for (*R*)-**3a** in 95% ee; HPLC analysis (Chiralpak IE, hexane/2-propanol = 65/35, flow rate 1.0 ml/min, λ= 225 nm) first peak: t_R = 14.2 min for (*R*), second peak: t_R = 32.8 min for (*S*).

3b; 70% yield (14.4 mg) with β-ICD, 59% yield (12.1 mg) with α-ICPN; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H) 7.46 (d, 1H, *J* = 5.2 Hz), 7.28-7.25 (m, 1H), 7.02 (t, 1H, *J* = 5.2 Hz), 6.84 (d, 1H, *J* = 5.2 Hz), 6.46 (s, 1H), 6.23 (s, 1H), 6.00 (s, 1H), 5.92-5.87 (m, 1H), 5.33 (dd, 1H, *J* = 11.6, 0.8 Hz), 5.24 (dd, 1H, *J* = 7.2, 0.8 Hz), 4.58 (d, 1 H, *J* = 10.4 Hz), 4.27 (d, 1H, *J* = 10.4 Hz), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 173.9, 154.0, 145.5, 142.8, 137.0, 131.2, 129.2, 129.0, 124.9, 122.9, 117.7, 109.3, 80.6, 63.3, 42.8, 28.1; HRMS (ESI) calcd for $C_{19}H_{22}N_2O_4Na^+$ 365.1472, found 365.1462; IR (KBr) *v* 3332, 2976, 2931, 2882, 1699, 1612, 1521, 1363, 1283, 1169, 762 cm^{-1}; $[\alpha]_D^{22}$ = -145.0 (*c* 0.7, $CHCl_3$) for (*S*)-**3b** in 96% ee; $[\alpha]_D^{22}$ = +105 (*c* 0.41, $CHCl_3$) for (*R*)-**3b** in 90% ee; HPLC analysis (Chiralpak IE, hexane/2-propanol = 65/35, flow rate 1.0 ml/min, λ = 212 nm) first peak: t_R = 10.8 min for (*R*), second peak: t_R = 22.1 min for (*S*).

3c; 52% yield (11.8 mg) with β-ICD, 37% yield (8.4 mg) with α-ICPN; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H) 7.60-7.40 (m, 6H), 7.22 (t, 1H, *J* = 8.0 Hz), 7.05 (t, 1H, *J* = 8.0 Hz), 6.79 (d, 1H, *J* = 8.0 Hz), 6.61 (s, 1H), 6.30 (s, 1H), 6.01 (s, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 173.8, 154.1, 145.9, 144.0, 137.0, 134.2, 129.7, 129.3, 128.6, 128.3, 126.8, 125.0, 123.2, 109.6, 80.7, 63.4, 28.2; HRMS (ESI) calcd for $C_{22}H_{22}N_2O_4Na^+$ 401.1472, found 401.1465; IR (KBr) *v* 3348, 2976, 1273, 1726, 1499, 1369, 1167, 758, 702, 607 cm^{-1}; $[\alpha]_D^{22}$ = -82.2 (*c* 0.3, $CHCl_3$) for (*S*)-**3c** in 98% ee; $[\alpha]_D^{24}$ = +122.6 (*c* 0.4, $CHCl_3$) for (*R*)-**3c** in 87% ee; HPLC analysis (Chiralpak IE, hexane/2-propanol = 60/40, flow rate 1.0 ml/min, λ = 212 nm) first peak: t_R = 11.6 min for (*R*), second peak: t_R = 32.6 min for (*S*).

3d; 48% yield (10.7 mg) with β-ICD, 44% yield (9.8 mg) with α-ICPN; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.46 (d, 1H, *J* = 8.0 Hz), 7.27 (td, 1H, *J* = 7.8, 2.1 Hz), 7.01 (td, 1H, *J* = 7.8, 2.1 Hz), 6.82 (d, 1H, *J* = 8.0 Hz), 6.42 (s, 1H), 6.20 (s, 1H), 5.95 (s, 1H), 5.22 (m, 1H), 4.55 (dd, 1H, *J* = 7.8, 6.4 Hz), 4.27 (dd, 1H, *J* = 7.8, 6.4 Hz), 1.83 (s, 3H), 1.74 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 173.7, 154.0, 145.4, 142.9, 136.85, 136.75, 129.24, 129.15, 124.9, 122.7, 118.2, 109.0, 80.5, 63.4, 38.6, 28.1, 25.6, 18.2; HRMS (ESI) calcd for $C_{21}H_{26}N_2O_4Na^+$ 393.1785, found 393.1778; IR (KBr) *v* 3359, 2970, 2921, 2340, 1711, 1610, 1489, 1366, 751, 598 cm^{-1}; $[\alpha]_D^{22}$ = -59.0 (*c* 0.4, $CHCl_3$) for (*S*)-**3d** in 95% ee; $[\alpha]_D^{26}$ = +107.6 (*c* 0.5, $CHCl_3$) for (*R*)-**3d** in 89% ee; HPLC analysis (Chiralpak IE, hexane/2-propanol = 60/40, flow rate 1.0 ml/min, λ = 212 nm) first peak: t_R = 10.6 min for (*R*), second peak: t_R = 22.9 min for (*S*).

3e; 68% yield (17.4 mg) with β-ICD, 74% yield (19.0 mg) with α-ICPN; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.44 (d, 1H, *J* = 2.4 Hz), 7.38-7.27 (m, 5H), 7.14 (dd, 1H, *J* = 8.0, 2.4 Hz), 6.62 (d, 1H, *J* = 8.4 Hz), 6.49 (s, 1H), 6.27 (s, 1H), 6.01 (s, 1H), 5.09 (d, 1H, *J* = 16.0 Hz), 4.89 (d, 1H, *J* = 16.0 Hz), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 173.9, 153.9, 145.0, 141.4, 137.7, 135.1, 130.5, 129.2, 128.8, 128.3, 127.8, 127.2, 125.2, 110.4, 81.0, 63.2, 44.5, 28.1; HRMS (ESI) calcd for $C_{23}H_{23}ClN_2O_4Na^+$ 449.1239, found 449.1231; IR (KBr) *v* 2964, 2926, 2860, 2357, 2329, 1708, 1484, 1363, 1254, 1167, 752 cm^{-1}; $[\alpha]_D^{25}$ = -147.0 (*c* 0.4, $CHCl_3$) for (*S*)-**3e** in 98% ee; $[\alpha]_D^{17}$ = +114.4 (*c* 0.3, $CHCl_3$) for (*R*)-**3e** in 87% ee; HPLC analysis (Chiralpak IE, hexane/2-propanol = 65/35, flow rate 1.0

ml/min, λ = 208 nm) first peak: t_R = 8.0 min for (*R*), second peak: t_R = 13.0 min for (*S*).

3f; 83% yield (21.3 mg) with β-ICD; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.39-7.26 (m, 6H), 6.97 (dd, 1H, *J* = 7.8, 1.6 Hz), 6.71 (d, 1H, *J* = 1.6 Hz), 6.47 (s, 1H), 6.26 (s, 1H), 5.98 (s, 1H), 5.09 (d, 1H, *J* = 15.6 Hz), 4.85 (d, 1H, *J* = 15.6 Hz), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 174.3, 154.0, 145.2, 144.0, 137.6, 135.04, 135.00, 128.9, 127.8, 127.3, 127.2, 125.9, 122.9, 110.0, 80.9, 62.9, 44.5, 28.1; HRMS (ESI) calcd for $C_{23}H_{23}ClN_2O_4Na^+$ 449.1239, found 449.1228; IR (KBr) *v* 3288, 2973, 1707, 1608, 1488, 1371, 1278, 1171, 876 cm^{-1}; $[\alpha]_D^{20}$ = -121.0 (*c* 1.1, $CHCl_3$) for (*S*)-**3f** in 98% ee; HPLC analysis (Chiralpak IE, hexane/2-propanol = 65/35, flow rate 1.0 ml/min, λ = 263 nm) first peak: t_R = 8.4 min for (*R*), second peak: t_R = 15.5 min for (*S*).

3g; 81% yield (20.7 mg) with β-ICD; 44% yield (11.3 mg) with α-ICPN; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.39-7.29 (m, 5H), 7.26-7.23 (m, 1H), 7.18 (dd, 1H, *J* = 8.0, 0.8 Hz), 6.97-6.95 (m, 1H), 6.35 (s, 1H), 6.21 (s, 1H), 6.12 (s, 1H), 5.47 (d, 1H, *J* = 16.4 Hz), 5.36 (d, 1H, *J* = 16.4 Hz), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 174.9, 153.9, 145.0, 138.9, 137.9, 137.5, 132.0, 131.9, 128.5, 127.1, 126.6, 123.8, 123.2, 115.6, 80.9, 63.0, 45.5, 28.1; HRMS (ESI) calcd for $C_{23}H_{23}ClN_2O_4Na^+$ 449.1239, found 449.1229 IR (KBr) *v* 3342, 2976, 1721, 1496, 1455, 1366, 1162, 734 cm^{-1}; $[\alpha]_D^{23}$ = -88.2 (*c* 1.0, $CHCl_3$) for (*S*)-**3g** in 97% ee, $[\alpha]_D^{22}$ = + 113.9 (*c* 0.4, $CHCl_3$) for (*R*)-**3g** in 94% ee; HPLC analysis (Chiralpak IE, hexane/2-propanol = 65/35, flow rate 1.0 ml/min, λ = 216 nm) first peak: t_R = 8.7 min for (*R*), second peak: t_R = 17.6 min for (*S*).

3h; 73% yield (20.6 mg) with β-ICD, 79% yield (22.3 mg) with α-ICPN; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.57 (d, 1H, *J* = 2.0 Hz), 7.37-7.28 (m, 6H), 6.57 (d, 1H, *J* = 8.0 Hz), 6.49 (s, 1H), 6.27 (s, 1H), 6.01 (s, 1H), 5.08 (d, 1H, *J* = 15.8 Hz), 4.89 (d, 1H, *J* = 15.8 Hz), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 173.8, 153.9, 145.0, 141.8, 137.7, 135.1, 132.1, 130.8, 128.8, 127.9, 127.8, 127.2, 115.7, 110.9, 81.0, 63.2, 44.4, 28.1; HRMS (ESI) calcd for $C_{23}H_{23}BrN_2O_4Na^+$ 493.0733, found 493.0721; IR (KBr) *v* 3342, 2979, 2926, 1721, 1606, 1367, 1254, 1162, 737 cm^{-1}; $[\alpha]_D^{22}$ = -114.1 (*c* 1.0, $CHCl_3$) for (*S*)-**3h** in 96% ee; $[\alpha]_D^{22}$ = +148.3 (*c* 1.5, $CHCl_3$) for (*R*)-**3h** in 88% ee; HPLC analysis (Chiralpak IE, hexane/2-propanol = 65/35, flow rate 1.0 ml/min, λ = 216 nm) first peak: t_R = 8.5 min for (*R*), second peak: t_R = 13.6 min for (*S*).

3i; 78% yield (19.2 mg) with β-ICD; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.37-7.32 (m, 4H), 7.29-7.24 (m, 2H), 6.87 (td, 1H, *J* = 6.0, 2.0 Hz), 6.62 (dd, 1H, *J* = 5.6, 2.8 Hz), 6.50 (s, 1H), 6.28 (s, 1H), 6.00 (s, 1H), 5.11 (d, 1H, *J* = 10.4 Hz), 4.87 (d, 1H, *J* = 10.4 Hz), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 174.1, 159.2 (d, $^1J_{CF}$ = 159.9 Hz), 153.9, 145.0, 138.7, 137.8, 135.2, 130.4 (d, $^3J_{CF}$ = 4.8 Hz), 128.8, 127.7, 127.2, 115.5 (d, $^2J_{CF}$ = 15.3 Hz), 113.1 (d, $^2J_{CF}$ = 16.8 Hz), 110.0 (d, $^3J_{CF}$ = 5.8 Hz), 80.9, 63.4, 44.5, 28.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ -119.5; HRMS (ESI) calcd for $C_{23}H_{23}FN_2O_4Na^+$ 433.1534, found 433.1527; IR (KBr) *v* 3299, 2980, 1732, 1709, 1525, 1490, 1367, 1264, 1164 cm^{-1}; $[\alpha]_D^{23}$ = -99.4 (*c* 0.9, $CHCl_3$) for (*S*)-**3i** in 98% ee; HPLC analysis (Chiralpak IE, hexane/2-propanol = 65/35, flow rate 1.0 ml/min, λ = 216 nm) first peak: t_R = 8.6 min for (*R*), second peak: t_R = 14.6 min for (*S*).

3j; 77% yield (18.8 mg) with β-ICD, 58% yield (14.1 mg) with α-ICPN; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.38-7.24 (m, 6H), 6.98 (d, 1H, *J* = 8.0 Hz), 6.60 (d, 1H, *J* = 8.0 Hz), 6.42 (s, 1H), 6.21 (s, 1H), 6.06 (s, 1H), 5.11 (d, 1H, *J* = 15.6 Hz), 4.86 (d, 1H, *J* = 15.6 Hz), 2.26 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 174.2, 154.0, 145.5, 140.2, 137.2, 135.7, 132.6, 129.6, 129.0, 128.7, 127.5, 127.2, 125.5, 109.2, 80.6, 63.5, 44.3, 28.1, 21.1; HRMS (ESI) calcd for $C_{24}H_{26}N_2O_4Na^+$ 429.1785, found 429.1776; IR (KBr) *v* 3419, 2976, 2926, 1715, 1497, 1367, 1164, 997, 805 cm^{-1}; $[\alpha]_D^{22}$ = -157.0 (*c* 0.3, $CHCl_3$) for (*S*)-**3j** in 95% ee; $[\alpha]_D^{24}$ = +122.1 (*c* 0.25, $CHCl_3$) for (*R*)-**3j** in 96% ee; HPLC analysis (Chiralpak IE, hexane/2-propanol = 65/35, flow rate 1.0 ml/min, λ = 262 nm) first peak: t_R = 13.0 min for (*R*), second peak: t_R = 28.3 min for (*S*).

3k; 57% yield (10.8 mg) with β-ICD, 45% yield (8.5 mg) with α-ICPN; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H) 7.45 (dd, 1H, *J* = 7.2, 0.8 Hz), 7.31 (td, 1H, *J* = 7.2, 0.8 Hz), 7.03 (td, 1H, *J* = 7.2, 0.8 Hz), 6.86 (d, 1H, *J* = 7.2 Hz), 6.43 (s, 1H), 6.21 (s, 1H), 5.98 (s, 1H), 3.30 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 174.2, 154.0, 145.4, 143.5, 137.0, 129.4, 129.1, 124.7, 123.0, 108.4, 80.6, 63.4, 28.1, 26.7; HRMS (ESI) calcd for $C_{17}H_{20}N_2O_4Na^+$ 339.1315, found 339.1306; IR (KBr) *v* 3304, 2976, 1712, 1613, 1483, 1371, 1252, 1166, 756 cm^{-1}; $[\alpha]_D^{23}$ = -108.0 (*c* 0.5, $CHCl_3$) for (*S*)-**3k** in 95% ee; $[\alpha]_D^{19}$ = + 129.2 (*c* 0.6, $CHCl_3$) for (*R*)-**3k** in 83% ee; HPLC analysis (Chiralpak IE, hexane/2-propanol = 65/35, flow rate 1.0 ml/min, λ = 216 nm) first peak: t_R = 13.3 min for (*R*), second peak: t_R = 24.7 min for (*S*).

3l; Analytical datas were well matched with reported value.[5] 39% yield (9.9 mg), 31% ee; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, 1H, *J* = 7.2 Hz), 7.37-7.26 (m, 4H), 7.24-7.20 (m, 2H), 7.01 (td, 1H, *J* = 7.6, 0.8 Hz), 6.76 (d, 1H, *J* = 7.6 Hz), 6.37 (s, 1H), 6.03 (s, 1H), 5.91 (s, 1H), 5.09 (s, 2H), 3.15 (s, 3H), 1.30 (s, 9H); $[\alpha]_D^{24}$ = -30.4 (*c* 0.68, CH_2Cl_2) for (*S*)-**3l** in 31% ee (lit.[5] $[\alpha]_D^{25}$ = -76.3 (*c* 0.68, CH_2Cl_2) for (*S*)-**3l** in 87% ee); HPLC analysis (Chiralpak OD-H, hexane/2-propanol = 9/1, flow rate 1.0 ml/min, λ = 236 nm) first peak: t_R = 10.7 min for (*R*), second peak: t_R = 13.9 min for (*S*).

Preparation of 7 from 3: To stirred **3k** (0.050 mmol) in THF (0.5 mL) was added to DIBAL in THF (0.10 mmol, 0.1 mL) under -78 °C. After 1 h, aq. HCl (1.0 M, 0.5 mL) was added and extracted with ethylacetate. After dried in *vacuo*, resulting crude product was purified by silica gel column chromatography using hexane/ethyl acetate as eluent to provide product **7a**. The procedures for preparation **7a**–**7b** from **3a**, **3l** are similar to that of preparation **7a** from **3k**, using DIBAL (0.10–0.13 mmol).

7a; 50% yield (8.0 mg) from **3k;** 44% yield (7.0 mg) from **3l**; White solid; M.p. = 142-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.26 (m, 2H), 7.10 (t, 1H, *J* = 7.6 Hz), 6.84 (d, 1H, *J* = 7.6 Hz), 6.30 (s, 1H), 5.26 (s, 1H), 4.94 (s, 1H), 4.60-4.45 (m, 1H), 4.33-4.21 (m, 1H), 3.21 (s,

3H), 2.80-2.70 (m, 1H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 153.9, 143.7, 143.5, 130.1, 129.0, 124.1, 122.9, 118.8, 108.3, 80.3, 65.7, 63.8, 28.0, 26.6; HRMS (ESI) calcd for $C_{17}H_{22}N_2O_4Na^+$ 341.1472, found 341.1466; IR (KBr) *v* 3354, 2970, 2931, 2357, 1709, 1611, 1497, 1365, 1256, 1170, 1014, 795, 752 cm^{-1}. $[\alpha]_D^{17}$ = +46.3 (*c* 0.6, $CHCl_3$) for (*S*)-**7a** in 94% ee ($[\alpha]_D^{17}$ = +12.2 (*c* 0.5, $CHCl_3$) for (*S*)-**7a** in 31% ee); HPLC analysis (Chiralpak IE, hexane/2-propanol = 60/40, flow rate 1.0 ml/min, λ = 240 nm) first peak: t_R = 8.2 min for (*R*), second peak: t_R = 9.4 min for (*S*).

7b; 51% yield (10.1 mg); White solid; M.p. = 164-165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.15 (m, 4H), 7.06 (t, 1H, *J* = 7.6 Hz), 6.70 (d, 1H, *J* = 7.6 Hz), 6.49 (brs, 1H), 5.30 (s, 1H), 5.14 (brd, 1H, *J* = 10.8 Hz), 4.95 (s, 1H), 4.71 (br, 1H), 4.58 (dd, 1H, *J* = 12.8, 4.8 Hz), 4.32 (dd, 1H, *J* = 12.8, 2.8 Hz), 2.91 (s, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 154.0, 143.9, 142.6, 135.7, 128.9, 128.7, 127.5, 127.1, 124.0, 122.9, 118.8, 109.3, 80.4, 65.8, 63.8, 44.0, 28.1; HRMS (ESI) calcd for $C_{23}H_{26}N_2O_4Na^+$ 417.1785, found 417.1774; IR (KBr) *v* 3458, 3337, 2970, 2361, 1699, 1500, 1364, 1173, 1003, 749 cm^{-1}. $[\alpha]_D^{24}$ = + 27.5 (*c* 1.0, $CHCl_3$) for (*S*)-**7b** in 97 % ee; HPLC analysis (IE, hexane/2-propanol = 70/30, flow rate 1.0 ml/min, λ = 214 nm) first peak: t_R = 9.8 min for (*R*), second peak: t_R = 11.5 min for (*S*).

Preparation of 9: A mixture of **7b** (0.038 mmol), 4-DMAP (1.92 μmol) and Ac_2O (0.077 mmol) in pyridine (0.19 mL) was stirred at rt for 14 h. The reaction mixture was directly purified by silica gel column chromatography using hexane/ethyl acetate as eluent to provide product **9** as colorless oil.

9; 69% yield (11.4 mg); Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.25 (m, 6H), 7.19 (td, 1H, *J* = 7.8 Hz, 1.1 Hz), 7.05 (td, 1H, *J* = 7.8 Hz, 1.1 Hz), 6.69 (d, 1H, *J* = 7.8 Hz), 6.09 (bs, 1H), 5.39 (s, 1H), 5.19 (s, 1H), 5.13-5.10 (m, 1H), 4.93 (d, 1H, *J* = 13.5 Hz), 4.72-4.69 (m, 2H), 2.05 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 170.8, 154.0, 142.8, 140.4, 135.7, 129.1, 128.7. 127.5, 127.1, 124.2, 122.8, 109.4, 80.6, 65.3, 63.3, 44.1, 28.2, 21.0; HRMS (ESI) calcd for $C_{25}H_{28}N_2O_5Na^+$ 459.1896, found 459.1884; IR (KBr) *v* 3346, 2977, 2351, 1722, 1614, 1489, 1369, 1242, 1172, 999, 757, 698 cm^{-1}. $[\alpha]_D^{25}$ = +14.3 (*c* 0.6, $CHCl_3$) in 97% ee; HPLC analysis (Chiralpak IE, hexane/2-propanol = 70/30, flow rate 1.0 ml/min, λ = 210 nm) first peak: t_R = 14.5 min for (*R*), second peak: t_R = 23.5 min for (*S*).

Acknowledgements

This study was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysis" from The Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan, the CREST project of the Japan Science and Technology Corporation (JST), and Advanced Catalytic Transformation Program for Carbon Utilization (ACT-C) of JST. Y. Y. thanks JSPS Research Fellowships for Young Scientists. We acknowledge the technical staff of the Comprehensive Analysis Center of ISIR, Osaka University (Japan).

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