Quinine-catalyzed enantioselective tandem conjugate addition / intramolecular cyclization of malononitrile and 1,4-dien-3-ones

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Abstract
An organocatalytic tandem conjugate addition / intramolecular cyclization of malononitrile and conformationally restricted 1,4-dien-3-ones has been developed. A series of cinchona alkaloids and their derivatives were examined as the catalysts. Quinine was found to be the most efficient catalyst in the absence of any additive. The reaction gave 2-amino-4*H*-pyrans with high yield and excellent enantiopurity using only 5 mol% quinine as the catalyst.

Keywords: Conjugate addition, tandem reaction, malononitrile, restricted dienones, quinine

Introduction

Recently pyrano[3,2-*c*]pyridone derivatives have received considerable attention due to their biological activities.[1] Compounds **4** (Figure 1) have been synthesized for the evaluation of various biologic activities.[2,3] Perumal and co-workers reported that racemic **4** showed significant inhibitory activity against *Mycobacterium tuberculosis* and multi-drug resistant tuberculosis.[1c] However the effect of the chiral center of **4** on its biological activity is still unknown. Recently, we developed an enantioselective cascade reaction of malononitrile and dienones.[4] Bicyclic pyrans **4** were prepared in excellent yields and enantioselectivities. Although *N*-[3,5-bis(trifluoromethyl)phenyl]-*N*'-[(*R*,*R*)-2-(1-piperidinyl)cyclohexyl]thiourea was found to be the efficient catalyst for the transformation, it is not commercially available and requires tedious synthesis. The drawback hinders our ongoing study of the biological activities of these compounds.

Over the past 10 years, asymmetric organocatalytic conjugate addition has emerged as a powerful and environmentally friendly tool for the production of chiral organic compounds.[5] The cascade reactions of organocatalytic conjugate additions proved to be an efficient method for the

synthesis of cyclic chiral compounds.[6] Cinchona alkaloids and their derivatives are proved to be highly effective and versatile in asymmetric catalysis.[7-9] Recently, we reported a cinchona alkaloid catalyzed highly enantioselective cascade reaction of malononitrile and α-substituted chalcones.[10] By using quinine as catalyst, the reaction gave 2-amino-4*H*-pyrans with excellent yields and enantioselectivities. Herein we report a cinchona alkaloid catalyzed conjugate addition of malononitrile to dienones **1**.

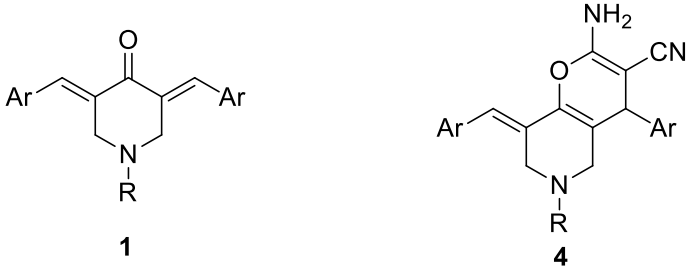
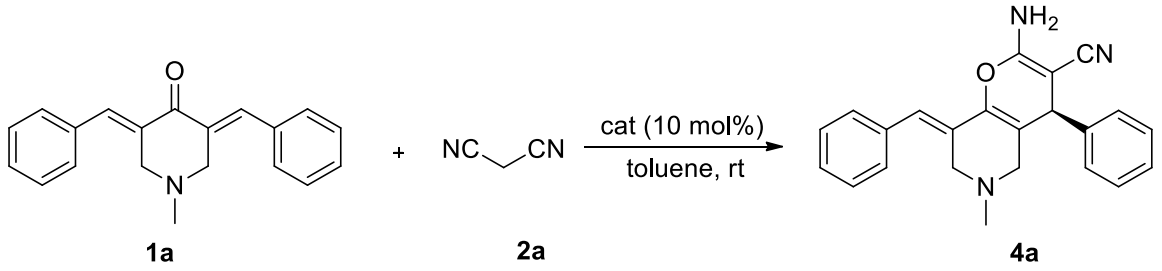


Figure 1. Dienones **1** and their derivative 2-amino-4*H*-pyrans **4**.

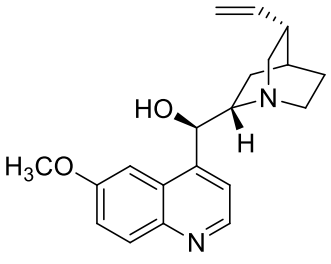
Results and Discussion

Initially, the reaction of (*E*,*E*)-1-methyl-3,5-bis(phenylmethylene)-4-piperidinone (**1a**) and malononitrile **2a** was studied. A series of cinchona alkaloids was examined and the results are summarized in Table 1. Bicyclic pyran **4a** was obtained in excellent yield and enantioselectivity by using quinine **3a** as the catalyst (Table 1, entry 1). The quinidine **3b** provided slightly dropped yield and moderate enantioselectivity (Table 1, entry 2). The 6′-methoxy group and the configuration of catalyst were proved to be important for the enantioselectivity. Without 6′-methoxy group, cinchonine **3c** gave poor yield and enantioselectivity (Table 1, entry 3). Moderate yield and low enantioselectivity was obtained when cinchonidine **3d** was used (Table 1, entry 4). The 6′-demethyl quinine **3e** and 6′-demethyl-9-benzyloxyquinine **3f**[11] gave racemic **4a** with moderate to excellent yield (Table 1, entries 5–6). Cinchona alkaloid derivative $(DHQD)_2PHAL$ **3g**[12] (Table 1, entry 7) gave poor reactivity and enantioselectivity.

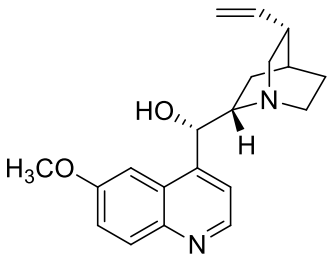
Table 1. Catalyst screening[a]



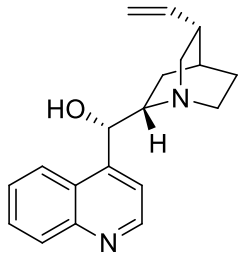
1a **2a** **4a**



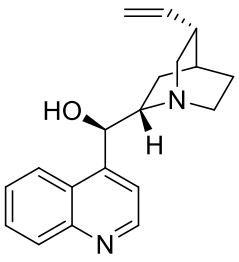
3a (quinine)



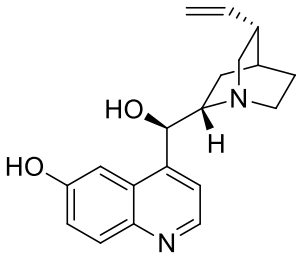
3b (quinidine)



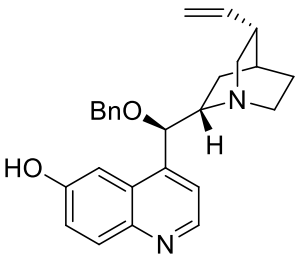
3c (cinchonine)



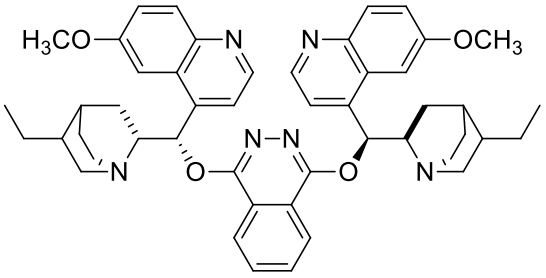
3d (cinchonidine)



3e



3f



3g ((DHQD)$_2$PHAL)

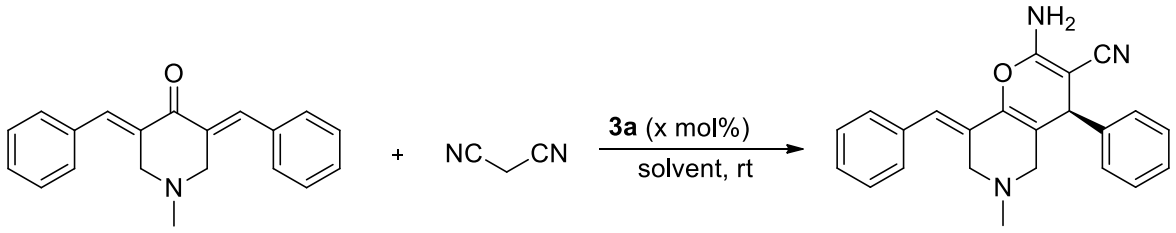
Entry	Catalyst	Time (h)	Yield (%)[b]	ee (%)[c]
1	**3a**	22	94	88
2	**3b**	24	90	-51
3	**3c**	96	30	0
4	**3d**	72	73	44
5	**3e**	72	58	0
6	**3f**	72	93	0
7	**3g**	72	30	38

[a.]The reactions were carried out with **1a** (0.100 mmol), **2a** (0.150 mmol) and **cat** (0.010 mmol) in toluene (1 mL) at rt. [b.]Isolated yields by centrifugation. [c.]Determined by chiral HPLC.

Using **3a** as the catalyst, a number of reaction solvents was screened and the results are

summarized in Table 2. Significant effect of the reaction solvent on the yield and enantioselectivity was observed. Low yields and enantioselectivities were obtained in hexane, dichloromethane, chloroform and 1,4-dioxane (Table 2, entries 1–4). Protic solvent ethanol provided moderate yield but poor enantioselectivity (Table 2, entry 5). Moderate to good yield and enantioselectivity were achieved in tetrachloromethane (Table 2, entry 6), and toluene was found to be the best reaction solvent (Table 2, entry 7). The effects of other reaction conditions were also studied. When the loading of **3a** was increased to 20 mol%, the reaction time was a little shortened with similar yield and enantioselectivity. Improved enantioselectivity was obtained by decreasing the loading of **3a** to 5 mol%. Further on decreasing the loading to 2 mol%, longer reaction time was required together with a lower yield.

Table 2. Optimization of reaction conditions[a]



1a **2a** **4a**

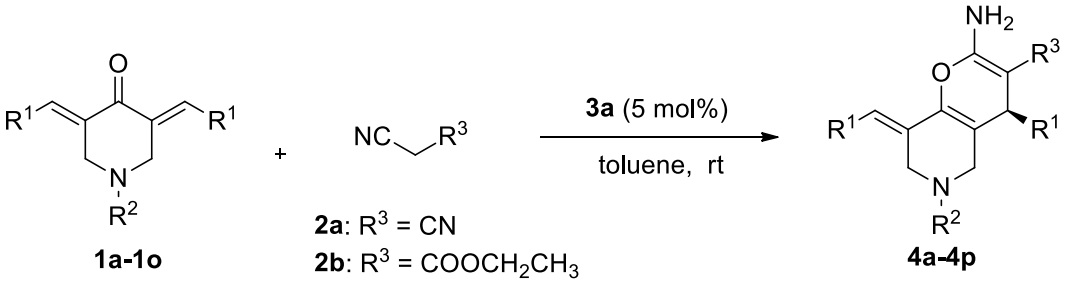
Entry	Solvent	**3a** (x mol%)	Time (h)	Yield (%)[b]	ee (%)[c]
1	Hexane	10	96	58	5
2	CH_2Cl_2	10	96	79	52
3	$CHCl_3$	10	96	58	61
4	1,4-dioxane	10	96	33	54
5	EtOH	10	8	88	0
6	CCl_4	10	10	85	72
7	Toluene	10	22	99	86
8	Toluene	10	22	94[d]	88
9	Toluene	20	16	99[d]	86
10	Toluene	5	26	93[d]	91
11	Toluene	2	96	85[d]	90

[a] The reactions were carried out with **1a** (0.100 mmol), **2a** (0.150 mmol) and **3a** in solvent (1 mL) at rt. [b] Isolated yields by column chromatography. [c] Determined by chiral HPLC. [d] Isolated yields by centrifugation.

The substrate scope of this reaction was examined and the results are summarized in Table 3. In general, both electron-withdrawing and electron-donating groups on the phenyl residues of the dienones were tolerated very well (Table 3, entries 2–7). Compared with electron-donating groups substituted dienones **1b,c**, the halogen and electron-withdrawing groups substituted

dienones **1d-g** gave higher yields, but a slightly lower enantioselectivities. *m*-Chloro and *m*-nitro substitutions led to excellent yields but moderate enantioselectivities (Table 3, entries 8–9). *o*-Chloro and *o*-methoxy substitution also gave excellent yields and moderate to good enantioselectivities (Table 3, entries 10–11). Good yields and moderate enantioselectivities were obtained after longer reaction time when the phenyl group was replaced with thiophene and cinnamyl group (Table 3, entries 12–13). (*E*,*E*)-3,5-Bis(cyclohexylmethylene)-1-methyl-4-piperidinone (**1n**) was also applicable: good yield and enantioselectivity were obtained using 20 mol% **3a** after extended reaction time (Table 3, entry 14). The benzyl substitution at N atom provided good yield and enantioselectivity (Table 3, entry 15). Low yield and moderate enantioselectivity were obtained when ethyl cyanacetate **2b** was used (Table 3, entry 16).

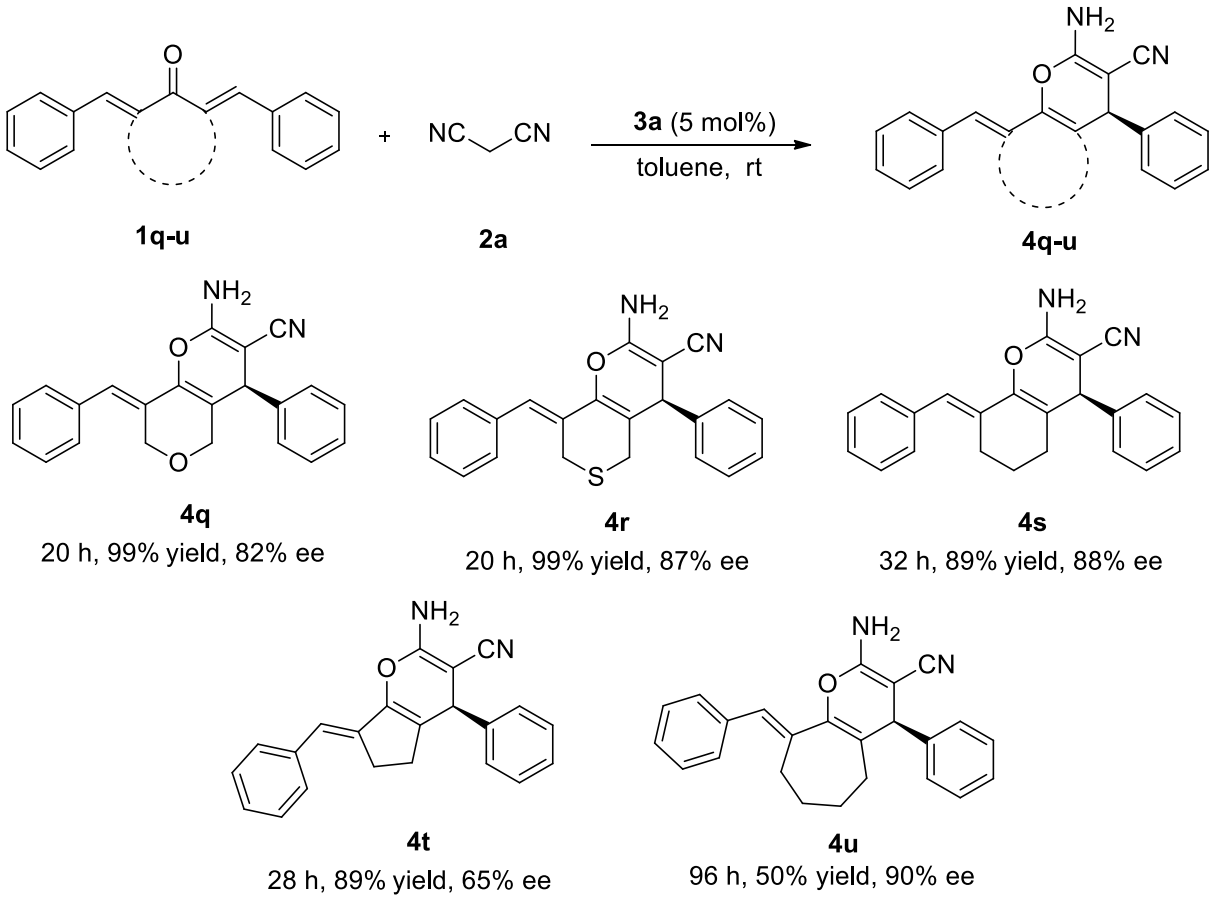
Table 3. Reactions of **2** with dienones **1a-o**[a]



Entry	R^1, R^2 (**1**)	**2**	Time (h)	Yield (%)[b]	ee (%)[c]
1	Phenyl, CH_3 (**1a**)	**2a**	26	**4a**, 93[d]	91
2	4-Me-phenyl, CH_3 (**1b**)	**2a**	48	**4b**, 77	86
3	4-MeO-phenyl, CH_3 (**1c**)	**2a**	56	**4c**, 86[d]	84
4	4-Cl-phenyl, CH_3 (**1d**)	**2a**	36	**4d**, 99	76
5	4-Br-phenyl, CH_3 (**1e**)	**2a**	30	**4e**, 90	80
6	4-F-phenyl, CH_3 (**1f**)	**2a**	42	**4f**, 96	78
7	4-NO_2-phenyl, CH_3 (**1g**)	**2a**	96	**4g**, 99[d]	60
8	3-Cl-phenyl, CH_3 (**1h**)	**2a**	36	**4h**, 99	72
9	3-NO_2-phenyl, CH_3 (**1i**)	**2a**	72	**4i**, 99[d]	60
10	2-Cl-phenyl, CH_3 (**1j**)	**2a**	36	**4j**, 99	73
11	2-MeO-phenyl, CH_3 (**1k**)	**2a**	30	**4k**, 99	80
12	Thiophen-2-yl, CH_3 (**1l**)	**2a**	96	**4l**, 88[d]	64
13	*E*-styryl, CH_3 (**1m**)	**2a**	120	**4m**,73[d]	64
14[e]	cyclohexyl, CH_3 (**1n**)	**2a**	80	**4n**, 90	86
15	phenyl, Bn (**1o**)	**2a**	40	**4o**, 75	88
16[e]	phenyl, CH_3 (**1a**)	**2b**	120	**4p**, 30	70

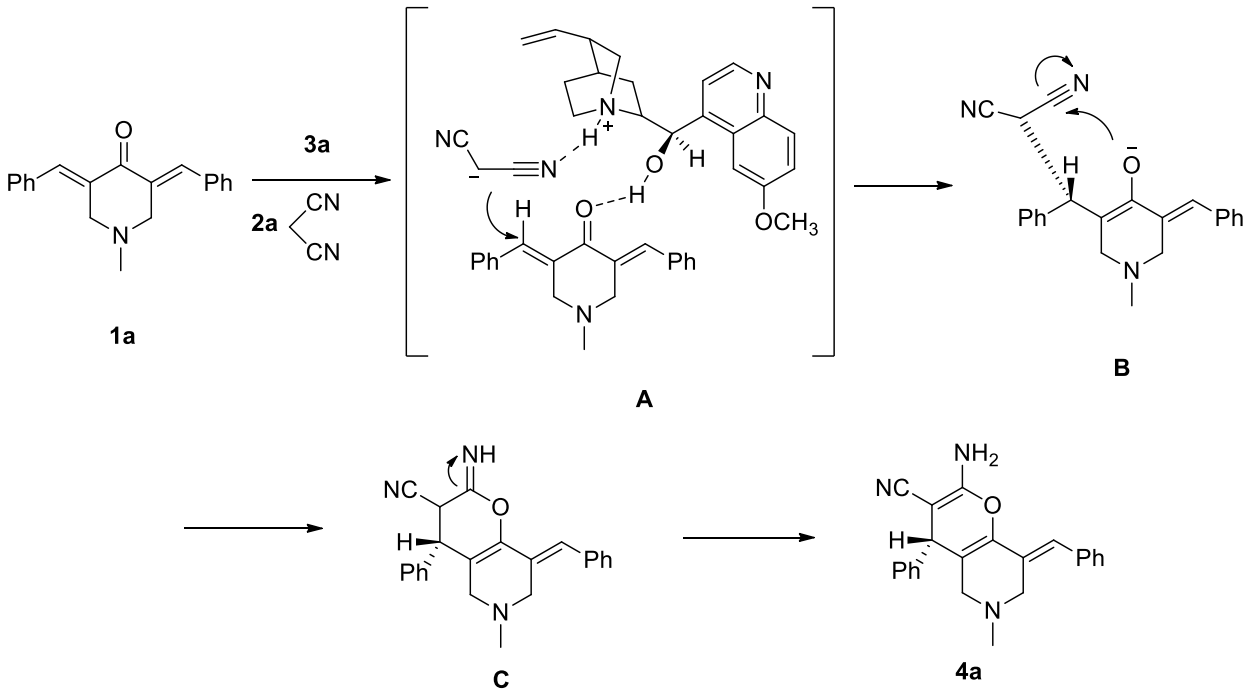
[a] The reactions were carried out with **1** (0.100 mmol), **2** (0.150 mmol) and **3a** (0.005 mmol) in toluene (1 mL) at rt. [b] Isolated yields by flash column chromatography unless otherwise indicated. [c] Determined by chiral HPLC. [d] Isolated yields by centrifugation. [e] 20 mol% **3a** was used.

The absolute configuration of **4** was assigned as (*S*) except for **4r** which was assigned as (*R*) by the comparison of the specific optical rotation with our previous report.[4] A number of other cyclic 1,5-diphenyl-1,4-pentadien-2-ones was also examined and the results are summarized in Scheme 1. Excellent yields and good enantioselectivities were achieved with **1q-s** (Scheme 1). (*E*,*E*)-2,5-Bis(phenylmethylene)cyclopentanone (**1t**) provided excellent yield and moderate enantioselectivity. When dienone **1u** was used, **4u** was obtained with excellent enantioselectivity but in a low yield.



Scheme 1. Reactions of malononitrile **2a** with dienones **1q-u**.

A bifunctional catalytic mechanism of quinine **3a** is illustrated in Scheme 2. A plausible transition state **A** of bifunctional activation is shown.[10] Malononitrile **2a** is deprotonated by quinine to form an anion. The H-bond interaction between the hydroxyl group of quinine and the carbonyl group helps to activate the enone. In addition, a H-bond interaction occurs between the nitrogen atom of malononitrile anion and the ammonium group. The attack of malononitrile anion from the *si*-face of dienone gives the chiral intermediate **B**. Then the intramolecular cyclization of intermediate **B** and subsequent tautomerization of **C** provide product **4a**.



Scheme 2. Proposed catalytic mechanism.

Conclusions

We have developed a highly enantioselective tandem conjugate addition / intramolecular cyclization of malononitrile **2a** with dienones **1a-o,q-u**. Quinine **3a** was proved to be the most efficient catalyst for the reaction without any additive. Generally excellent enantioselectivities and yields were obtained for a number of dienones with various substitutents and different ring sizes. Further studies on the bioactivity of the enantiopure products and other relative reactions are currently under way in our group.

Experimental Section

General. All solvents were used as commercial anhydrous grade without further purification. The flash column chromatography was carried out over silica gel (230–400 mesh), purchased from Qingdao Haiyang Chemical Company. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer as solutions in $CDCl_3$. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm, δ) downfield from the internal standard Me_4Si (TMS, δ = 0 ppm). Chemical shifts in ^{13}C NMR spectra are reported relative to the central line of the

chloroform signal (δ 77.0 ppm). Peaks are labeled as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Optical rotations were measured on a Perkin Elmer 341 digital polarimeter. Melting points were measured on a WRS-2A melting point apparatus and are uncorrected. High-resolution mass spectra were obtained with the SHIMADZU LCMS-IT-TOF mass spectrometer. The low resolution mass spectra were obtained at Agilent 6120 (Quadrupole LC-MS) mass spectrometer. Infrared (IR) spectra were recorded on a Bruker Tensor 37 spectrophotometer. Data are represented as frequency of absorption (cm^{-1}). Enantiomeric excesses of compounds were determined by HPLC using a Daicel Chiralpak AD-H column.

Typical procedure for the synthesis of racemic products. A mixture of (*E*,*E*)-1-methyl-3,5-bis(phenylmethylene)-4-piperidinone (**1a**) (28.9 mg, 0.100 mmol), malononitrile **2a** (9.9 mg, 0.150 mmol) and piperidine (8.5 mg, 0.100 mmol) in ethanol (1 mL) was stirred for 30 minutes at room temperature. The precipitate was filtered to provide racemic **4a** as a white solid (80% yield).

Typical procedure for organocatalytic conjugate addition of malononitrile 2a to dienones. A mixture of (*E*,*E*)-1-methyl-3,5-bis(phenylmethylene)-4-piperidinone (**1a**) (28.9 mg, 0.100 mmol), malononitrile **2a** (9.9 mg, 0.150 mmol) and quinine **3a** (3.3 mg, 0.005 mmol) in toluene (1 mL) was stirred for 26 h at room temperature. The white precipitate **4a** was collected by centrifugation.

(4*S*,8*E*)-2-Amino-5,6,7,8-tetrahydro-6-methyl-4-phenyl-8-(phenylmethylene)-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4a).[4] White solid, mp 191–194 °C. $[\alpha]_D^{20}$ -5.7 (c 0.13, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.39–7.21 (m, 10 H), 6.90 (s, 1 H), 4.56 (s, 2 H), 4.03 (s, 1 H), 3.58 (d, *J* 13.8 Hz, 1 H), 3.38 (d, *J* 13.6 Hz, 1 H), 2.97 (d, *J* 16.0 Hz, 1 H), 2.75 (d, *J* 15.8 Hz, 1 H), 2.26 (s, 1 H); MS (ESI): *m*/*z* 356.2 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 30 : 70, 254 nm, 0.8 mL/min), t_R(minor) 6.9 min, t_R(major) 11.7 min, 91% ee.

(4*S*,8*E*)-2-Amino-5,6,7,8-tetrahydro-6-methyl-4-(4-methylphenyl)-8-(4-methylphenylmethylene)-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4b).[4] White solid, mp 215 °C. $[\alpha]_D^{20}$ -14.3 (c 0.11, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.21–7.07 (m, 8 H), 6.86 (s, 1 H), 4.55 (s, 2 H), 3.98 (s, 1 H), 3.58 (d, *J* 13.7 Hz, 1 H), 3.37 (d, *J* 13.8 Hz, 1 H), 2.95 (d, *J* 16.0 Hz, 1 H), 2.75 (d, *J* 15.9 Hz, 1 H), 2.36 (s, 1 H), 2.33 (s, 1 H), 2.26 (s, 1 H); MS (ESI): *m*/*z* 384.2 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 30 : 70, 254 nm, 0.8 mL/min), t_R(minor) 6.4 min, t_R(major) 13.3 min, 86% ee.

(4*S*,8*E*)-2-Amino-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-8-(4-methoxyphenylmethylene)-6-methyl-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4c).[4] White solid, mp 185–187°C. $[\alpha]_D^{20}$ -8.9 (c 0.11, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.18–7.15 (m, 4 H), 6.91– 6.86 (m, 4 H), 6.83 (s, 1 H), 4.52 (s, 2 H), 3.97 (s, 1 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.57 (d, *J* 13.7 Hz, 1 H), 3.37 (d, *J* 13.8 Hz, 1 H), 2.94 (d, *J* 15.8 Hz, 1 H), 2.74 (d, *J* 15.8 Hz, 1 H), 2.27 (s, 1 H); MS (ESI): *m*/*z* 416.2 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 30 : 70, 254 nm, 0.8 mL/min), t_R(minor) 11.9 min, t_R(major)

22.1 min, 84% ee.

(4*S*,8*E*)-2-Amino-4-(4-chlorophenyl)-8-(4-chlorophenylmethylene)-5,6,7,8-tetrahydro-6-methyl-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4d).[4] White solid, mp 205–207 °C. $[\alpha]_D^{20}$ -12.8 (c 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.32 (m, 4 H), 7.21–7.13 (m, 4 H), 6.84 (s, 1 H), 4.57 (s, 2 H), 4.02 (s, 1 H), 3.51 (d, *J* 13.8 Hz, 1 H), 3.35 (d, *J* 13.6 Hz, 1 H), 2.94 (d, *J* 16.0 Hz, 1 H), 2.72 (d, *J* 16.0 Hz, 1 H), 2.27 (s, 1 H); MS (ESI): *m*/*z* 424.1 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 30 : 70, 254 nm, 0.8 mL/min), t_R(minor) 7.6 min, t_R(major) 9.7 min, 76% ee.

(4*S*,8*E*)-2-Amino-4-(4-bromophenyl)-8-(4-bromophenylmethylene)-5,6,7,8-tetrahydro-6-methyl-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4e).[4] White solid, mp 223–225 °C. $[\alpha]_D^{20}$ -13.9 (c 0.11, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.47 (m, 4 H), 7.11 (dd, *J* 22.0, 8.4 Hz, 4H), 6.81 (s, 1 H), 4.57 (s, 2 H), 4.00 (s, 1 H), 3.50 (d, *J* 13.7 Hz, 1 H), 3.33 (d, *J* 13.7 Hz, 1 H), 2.93 (d, *J* 15.9 Hz, 1 H), 2.71 (d, *J* 15.9 Hz, 1 H), 2.27 (s, 1 H); MS (ESI): *m*/*z* 514.0 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 30 : 70, 254 nm, 0.8 mL/min), t_R(minor) 7.8 min, t_R(major) 9.7 min, 80% ee.

(4*S*,8*E*)-2-Amino-4-(4-fluorophenyl)-8-(4-fluorophenylmethylene)-5,6,7,8-tetrahydro-6-methyl-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4f).[4] White solid, mp 197–198 °C. $[\alpha]_D^{20}$ -5.0 (c 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.17 (m, 4 H), 7.08–7.02 (m, 4 H), 6.86 (s, 1 H), 4.55 (s, 2 H), 4.03 (s, 1 H), 3.52 (d, *J* 13.4 Hz, 1 H), 3.36 (d, *J* 13.0 Hz, 1 H), 2.95 (d, *J* 15.9 Hz, 1 H), 2.72 (d, *J* 15.4 Hz, 1 H), 2.28 (s, 1 H); MS (ESI): *m*/*z* 392.2 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 30 : 70, 254 nm, 0.8 mL/min), t_R(minor) 7.3 min, t_R(major) 10.2 min, 78% ee.

(4*S*,8*E*)-2-Amino-5,6,7,8-tetrahydro-6-methyl-4-(4-nitrophenyl)-8-(4-nitrophenylmethylene)-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4g).[4] Yellow solid, mp 214–217 °C. $[\alpha]_D^{20}$ -43.5 (c 0.09, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* 8.6 Hz, 4 H), 7.45 (d, *J* 8.7 Hz, 2 H), 7.38 (d, *J* 8.7 Hz, 2 H), 6.96 (s, 1 H), 4.69 (s, 2 H), 4.20 (s, 1 H), 3.53 (d, *J* 14.3 Hz, 1 H), 3.40 (d, *J* 14.6 Hz, 1 H), 3.01 (d, *J* 16.2 Hz, 1 H), 2.72 (d, *J* 16.4 Hz, 1 H), 2.29 (s, 1 H); MS (ESI): *m*/*z* 446.2 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 30 : 70, 254 nm, 0.8 mL/min), t_R(minor) 18.2 min, t_R(major) 21.1 min, 60% ee.

(4*S*,8*E*)-2-Amino-4-(3-chlorophenyl)-8-(3-chlorophenylmethylene)-5,6,7,8-tetrahydro-6-methyl-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4h).[4] White solid, mp 172–175 °C. $[\alpha]_D^{20}$ -3.7 (c 0.11, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.23 (m, 5 H), 7.21 (s, 1 H), 7.14 (dt, *J* 6.8, 1.9 Hz, 1 H), 7.10 (d, *J* 7.4 Hz, 1 H), 6.83 (s, 1 H), 4.60 (s, 2 H), 4.01 (s, 1 H), 3.53 (d, *J* 13.8 Hz, 1 H), 3.35 (d, *J* 14.0 Hz, 1 H), 2.96 (d, *J* 16.0 Hz, 1 H), 2.73 (d, *J* 15.9 Hz, 1 H), 2.29 (s, 1 H); MS (ESI): *m*/*z* 424.1 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 30 : 70, 254 nm, 0.8 mL/min), t_R(minor) 6.3 min, t_R(major) 11.9 min, 72% ee.

(4*S*,8*E*)-2-Amino-5,6,7,8-tetrahydro-6-methyl-4-(3-nitrophenyl)-8-(3-nitrophenylmethylene)-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4i).[4] Yellow solid, mp 200–202 °C. $[\alpha]_D^{20}$ -44.4 (c

0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20–8.09 (m, 4 H), 7.63–7.55 (m, 4 H), 6.98 (s, 1 H), 4.70 (s, 2 H), 4.21 (s, 1 H), 3.57 (d, *J* 13.0 Hz, 1 H), 3.40 (d, *J* 13.2 Hz, 1 H), 3.04 (d, *J* 15.6 Hz, 1 H), 2.72 (d, *J* 15.4 Hz, 1 H), 2.30 (s, 1 H); MS (ESI): *m*/*z* 446.2 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 30 : 70, 254 nm, 0.8 mL/min), t_R(minor) 10.6 min, t_R(major) 26.2 min, 60% ee.

(4*S*,8*E*)-2-Amino-4-(2-chlorophenyl)-8-(2-chlorophenylmethylene)-5,6,7,8-tetrahydro-6-methyl-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4j).[4] White solid, mp 208–210 °C. $[\alpha]_D^{20}$ -7.3 (c 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.32 (m, 4H), 7.20–7.13 (m, 4H), 6.84 (s, 1 H), 4.57 (s, 2 H), 4.02 (s, 1 H), 3.51 (d, *J* 13.7 Hz, 1 H), 3.35 (d, *J* 13.9 Hz, 1 H), 2.94 (d, *J* 16.0 Hz, 1 H), 2.72 (d, *J* 16.0 Hz, 1 H), 2.27 (s, 1 H); MS (ESI): *m*/*z* 424.1 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 30 : 70, 254 nm, 0.8 mL/min), t_R(minor) 7.6 min, t_R(major) 9.7 min, 73% ee.

(4*S*,8*E*)-2-Amino-5,6,7,8-tetrahydro-4-(2-methoxyphenyl)-8-(2-methoxyphenylmethylene)-6-methyl-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4k).[4] White solid, mp 179–180 °C. $[\alpha]_D^{20}$ +35.3 (c 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.20 (m, 3 H), 7.09 (dd, *J* 7.4, 1.1 Hz, 1H), 6.99–6.88 (m, 5 H), 4.65 (s, 1 H), 4.51 (s, 2 H), 3.853 (s, 3 H), 3.845 (s, 3 H), 3.45 (d, *J* 13.7 Hz, 1 H), 3.31 (d, *J* 13.8 Hz, 1 H), 3.01 (d, *J* 16.1 Hz, 1 H), 2.78 (d, *J* 16.0 Hz, 1 H), 2.23 (s, 1 H); MS (ESI): *m*/*z* 416.2 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 30 : 70, 254 nm), 0.8 mL/min), t_R(minor) 8.5 min, t_R(major) 12.4 min. 80% ee.

(4*S*,8*E*)-2-Amino-5,6,7,8-tetrahydro-6-methyl-4-(2-thienyl)-8-(2-thienylmethylene)-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4l).[4] White solid, mp 172–174 °C. $[\alpha]_D^{20}$ -16.7 (c 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* 4.9 Hz, 1 H), 7.24 (d, *J* 4.7 Hz, 1 H), 7.08 - 7.04 (m, 2 H), 6.99 (s, 1 H), 6.95–6.93 (m, 2 H), 4.61 (s, 2 H), 4.37 (s, 1 H), 3.76 (d, *J* 14.4 Hz, 1 H), 3.48 (d, *J* 14.4 Hz, 1 H), 3.05 (d, *J* 15.9 Hz, 1 H), 2.95 (d, *J* 15.8 Hz, 1 H), 2.38 (s, 1 H); MS (ESI): *m*/*z* 368.1 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AS-H column (*i*-PrOH : hexane 20 : 80, 254 nm, 0.8 mL/min), t_R(minor) 18.1 min, t_R(major) 21.0 min. 64% ee.

(4*S*,8*E*)-2-Amino-5,6,7,8-tetrahydro-6-methyl-4-[(1*E*)-2-phenylethenyl]-8-[(2*E*)-3-phenyl-2-propen-1-ylidene]-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4m).[4] Red solid, mp 169–181 °C. $[\alpha]_D^{20}$ -14.4 (c 0.42, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.24 (m, 10 H), 6.96 (dd, *J* 15.3, 11.6 Hz, 1 H), 6.70 (d, *J* 15.4 Hz, 1 H), 6.55 (d, *J* 11.8 Hz, 1 H), 6.51 (d, *J* 15.7 Hz, 1 H), 5.99 (dd, *J* 15.6, 8.9 Hz, 1 H), 4.58 (s, 2 H), 3.62 (d, *J* 8.9 Hz, 1 H), 3.57 (d, *J* 14.0 Hz, 1 H), 3.38 (d, *J* 13.9 Hz, 1 H), 3.14 (d, *J* 16.2 Hz, 1 H), 3.02 (d, *J* 16.0 Hz, 1 H), 2.44 (s, 1 H); MS (ESI): *m*/*z* 408.2 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK OD-H column (*i*-PrOH : hexane 20 : 80, 254 nm, 0.8 mL/min), t_R(major) 21.9 min, t_R(minor) 28.6 min, 64% ee.

(4*S*,8*E*)-2-Amino-4-cyclohexyl-8-(cyclohexylmethylene)-5,6,7,8-tetrahydro-6-methyl-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4n).[4] White solid, mp 185–188 °C. $[\alpha]_D^{20}$ -17.5 (c 0.13, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.57 (d, *J* 9.6 Hz, 1 H), 4.55 (s, 2 H), 3.36 (d, *J* 13.6 Hz,

1 H), 3.10 (d, *J* 15.2 Hz, 1 H), 2.95 (d, *J* 15.5 Hz, 1 H), 2.74 (d, *J* 1.9 Hz, 1 H), 2.41 (s, 1 H), 2.24–2.14 (m, 1 H), 1.80–0.99 (m, 21 H); MS (ESI): *m*/*z* 368.3 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 20 : 80, 254 nm, 0.8 mL/min), t_R(major) 5.0 min, t_R(minor) 5.5 min, 86% ee.

(4*S*,8*E*)-2-Amino-5,6,7,8-tetrahydro-4-phenyl-6-(phenylmethyl)-8-(phenylmethylene)-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4o).[4] White solid, mp 193–194 °C. $[\alpha]_D^{20}$ +18.2 (c 0.11, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.15 (m, 13 H), 7.10 (dd, *J* 6.5, 2.8 Hz, 2 H), 6.91 (s, 1 H), 4.56 (s, 2 H), 3.95 (s, 1 H), 3.76 (d, *J* 14.0 Hz, 1 H), 3.53–3.43 (m, 2 H), 3.46 (d, *J* 13.9 Hz, 1 H), 3.03 (d, *J* 16.2 Hz, 1 H), 2.85 (d, *J* 16.3 Hz, 1 H); MS (ESI): *m*/*z* 432.2 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 20 : 80, 254 nm, 0.8 mL/min), t_R(minor) 14.8 min, t_R(major) 17.0 min, 88% ee.

Ethyl (4*S*,8*E*)-2-amino-5,6,7,8-tetrahydro-6-methyl-4-phenyl-8-(phenylmethylene)-4*H*-pyrano[3,2-*c*]pyridine-3-carboxylate (4p).[4] White solid, mp 191–193 °C. $[\alpha]_D^{20}$ +17.9 (c 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.17 (m, 10 H), 7.00 (s, 1 H), 6.29 (brs, 2 H), 4.16 (s, 1 H), 4.01 (qd, *J* 7.1, 1.1 Hz, 2H), 3.69 (d, *J* 13.7 Hz, 1 H), 3.49 (d, *J* 13.7 Hz, 1 H), 3.21 (d, *J* 15.7 Hz, 1 H), 2.91 (d, *J* 16.1 Hz, 1 H), 1.09 (t, *J* 7.1 Hz, 1H); MS (ESI): *m*/*z* 403.2 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 30 : 70, 254 nm, 0.8 mL/min), t_R(minor) 7.7 min, t_R(major) 12.8 min, 70% ee.

(4*S*,8*E*)-2-Amino-7,8-dihydro-4-phenyl-8-(phenylmethylene)-4*H*,5*H*-pyrano[4,3-*b*]pyran-3-carbonitrile (4q).[4] White solid, mp 225–230 °C. $[\alpha]_D^{20}$ +20.8 (c 0.12, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43–7.21 (m, 10 H), 6.94 (s, 1 H), 6.91 (s, 2 H), 4.50 (dd, *J* 14.2, 1.1 Hz, 1 H), 4.17 (d, *J* 15.8 Hz, 1 H), 4.11 (s, 1 H), 3.73 (d, *J* 15.5 Hz, 1 H); MS (ESI): *m*/*z* 343.1 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 20 : 80, 254 nm, 0.8 mL/min), t_R(minor) 11.3 min, t_R(major) 16.5 min, 82% ee.

(4*R*,8*Z*)-2-Amino-7,8-dihydro-4-phenyl-8-(phenylmethylene)-4*H*,5*H*-thiopyrano[4,3-*b*]pyran-3-carbonitrile (4r).[4] White solid, mp 228–230 °C. $[\alpha]_D^{20}$ + 52.7 (c 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44–7.23 (m, 10 H), 7.16 (s, 1 H), 6.87 (s, 2 H), 4.08 (s, 1 H), 3.68–3.58 (m, 2 H), 3.26 (d, *J* 17.1 Hz, 1 H), 2.90 (d, *J* 17.0 Hz, 1 H); MS (ESI): *m*/*z* 359.1 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 20 : 80, 254 nm, 0.8 mL/min), t_R(minor) 10.7 min, t_R(major) 26.2 min, 87% ee.

(4*S*,8*E*)-2-Amino-5,6,7,8-tetrahydro-4-phenyl-8-(phenylmethylene)-4*H*-1-benzopyran-3-carbonitrile (4s).[4] White solid, mp 221–224 °C. $[\alpha]_D^{20}$ +26.8 (c 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.24 (m, 10 H), 6.88 (s, 1 H), 4.50 (s, 2 H), 3.97 (s, 1 H), 2.74–2.70 (m, 1 H), 2.60–2.56 (m, 1 H), 2.04–1.92 (m, 2 H), 1.63–1.60 (m, 2 H); MS (ESI): *m*/*z* 341.2 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 20 : 80, 254 nm, 0.8 mL/min), t_R(minor) 8.6 min, t_R(major) 20.1 min. 88% ee.

(4*S*,7*E*)-2-Amino-4,5,6,7-tetrahydro-4-phenyl-7-(phenylmethylene)cyclopenta[*b*]pyran-3-carbonitrile (4t).[4] White solid, mp 210–214 °C. $[\alpha]_D^{20}$ + 20.2 (c 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.20 (m, 10 H), 6.46 (s, 1 H), 4.64 (s, 2 H), 4.26 (s, 1 H), 2.97–2.28 (m, 2 H), 2.42–2.36 (m, 1 H), 2.27–2.21 (m, 1 H); MS (ESI): *m*/*z* 327.1 $[M + H]^+$; Enantiomeric excess

was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH : hexane 20 : 80, 254 nm, 0.8 mL/min), t_R(minor) 8.8 min, t_R(major) 12.7 min, 65% ee.

(4*S*,9*E*)-2-Amino-4,5,6,7,8,9-hexahydro-4-phenyl-9-(phenylmethylene)cyclohepta[*b*]pyran-3-carbonitrile (4u).[4] White solid, mp 175–179 °C. $[\alpha]_D^{20}$ +57.5 (c 0.11, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.25 (m, 10 H), 6.99 (s, 1 H), 4.48 (s, 2 H), 3.94 (s, 1 H), 2.71–2.65 (m, 1 H), 2.54–2.47 (m, 1 H), 2.18–2.11 (m, 1 H), 2.06–1.99 (m, 1 H), 1.81–1.67 (m, 3 H), 1.65–1.60 (m, 1 H); MS (ESI): *m*/*z* 355.2 $[M + H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH :hexane 10 : 90, 254 nm, 0.5 mL/min), t_R(minor) 8.0 min, t_R(major) 9.5 min, 90% ee.

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