JOC The Journal of Organic Chemistry

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Organocatalytic Conjugate Addition of Malononitrile to Conformationally Restricted Dienones

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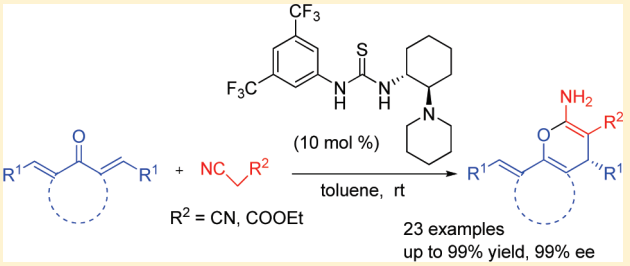
Supporting Information

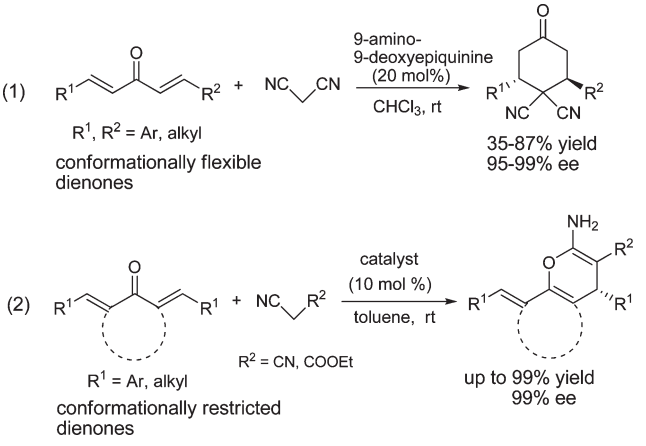
ABSTRACT: Organocatalytic conjugate addition of malononitrile to conformationally restricted dienones has been studied. A series of chiral primary and tertiary amine catalysts were screened. A piperidine-based thiourea-tertiary amine was found to be the efficient catalyst. Chiral pyran derivatives were obtained in excellent yields and enantioselectivities via a cascade conjugate addition−intramolecular cyclization pathway. The reaction is remarkably different for the corresponding reaction of conformationally flexible dienones.



INTRODUCTION

In the recent decade, great progress has been achieved in organocatalytic asymmetric reactions.[1] Among various organocatalytic reactions developed so far, organocatalytic conjugate additions have proven to be extremely powerful and diversified. A large number of Michael acceptors and nucleophilic reagents have been applied successfully.[2] In addition, cascade reactions triggered by organocatalytic conjugate addition provide highly efficient and convenient methods to construct polycyclic chiral compounds.[3] Recently we found that organocatalytic conjugate addition of malononitrile to dienones generated chiral cyclohexanones in excellent yields, diastereoselectivities, and enantioselectivities (Scheme 1, eq 1).[4] A mechanism of double conjugate addition was suggested to explain the experimenal results. Interestingly, in this study we observed only a trace amount of single conjugate addition product. We proposed that the consequent intramolecular conjugate addition proceeds faster than the first intermolecular conjugate addition. Thus, we become interested in the reaction of conformationally restricted dienones. When such substrates are adopted, the necessary conformation for the second intramolecular conjugate addition cannot be achieved, and the reaction should stop after the first conjugate addition. In this paper, we reported organocatalytic conjugate addition of malononitrile to conformationally restricted dienones. The reaction provided bicyclic pyran derivatives via new cascade steps (Scheme 1, eq 2). In addition, significantly different requirements of organocatalysts and reaction conditions were observed.

Scheme 1. Organocatalytic Conjugate Addition of Malononitrile to Dienones



RESULTS AND DISCUSSION

Recently malononitrile had been used as a useful nucleophilic reagent in asymmetric organocatalytic conjugate additions.[5] Moderate to good enantioselectivities were achieved for conjugate addition of malononitrile to chalcones.[5c−e] Initially we studied the reaction of 3,5-bis(benzylidene)-4-piperidone **1a** and malononitrile **2a**. A series of organocatalysts **3a**-**3h** (Scheme 2) were screened and the results are summarized in Table 1. 9-Amino-9-deoxyepiquinine (**3a**), which is the best catalyst in our previous study of conformationally flexible dienones,[4] was examined first. As expected, the reaction did not give the single conjugate addition product. Instead bicyclic pyran **4a** was obtained in poor yield and enantioselectivity (Table 1, entries 1−2). The product **4a** obviously generated from the primary conjugate addition intermediate through an

Received: January 18, 2011
Published: April 05, 2011

Scheme 2. Organocatalysts 3a−3i

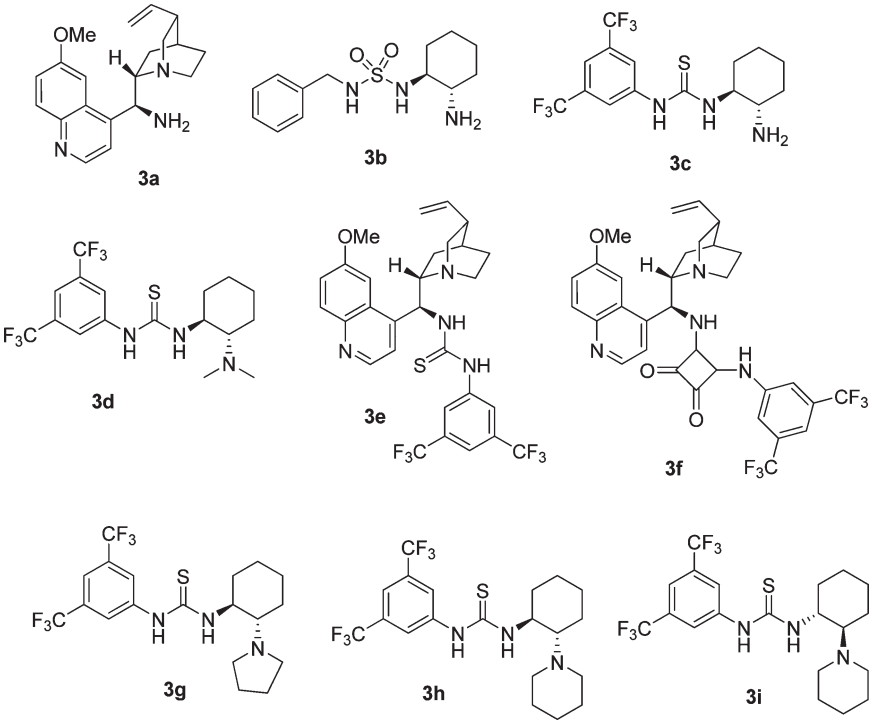
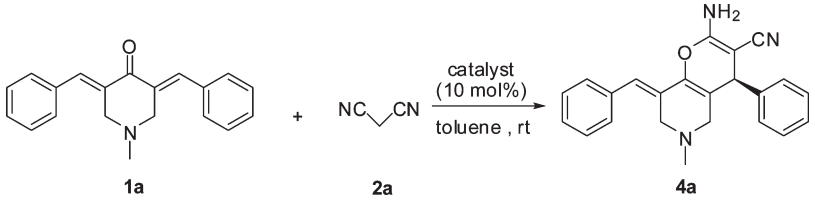


Table 1. Screening of Catalysts[a]



entry	catalyst	time (h)	yield (%)[b]	ee (%)[c]
1	**3a**	96	24	21
2[d]	**3a**	48	37	6
3	**3b**	96	30	2
4	**3c**	72	52	34
5	**3d**	72	89	85
6	**3e**	72	95	79
7	**3f**	96	95	77
8	**3g**	36	97	81
9	**3h**	72	95	96

[a] The reactions were carried out with **1a** (0.100 mmol), **2a** (0.105 mmol), and **3a**−**3h** (0.010 mmol) in toluene (1.0 mL) at room temperature. [b] Isolated yields by centrifugation. [c] Determined by chiral HPLC. [d] The reaction was carried out with 20 mol % **3a** and 40 mol % trifluoroacetic acid in $CHCl_3$ according to the optimum reaction conditions in ref 4.

intramolecular addition of enolate oxygen anion to the nitrile group and a consequent tautomerization. Similar cascade reaction was also reported in base-promoted addition of malononitrile to **1a**.[6] Compound **4a** is almost insoluble in toluene and was deposited as a white solid after the reaction. It could be readily obtained by the centrifugation. Perumal and co-workers reported that racemic **4a** and its analogues showed significant inhibitive activity against *Mycobacterium tuberculosis* and multidrug resistant *M. tuberculosis*.[6h] To the best of our knowledge, homochiral **4a** and its analogues have never been prepared. Currently, the effect of the chiral center on the biological activity of these compounds is unknown. We extended our screening to bifunctional chiral primary amine catalysts **3b**[7] and **3c**.[8] Again, only low yields and enantioselectivities were achieved (Table 1, entries 3−4). We turned our attention to chiral tertiary amine catalysts. Takemoto's catalyst **3d** was demonstrated to be a better choice for this reaction.

dx.doi.org/10.1021/jo200112r |*J. Org. Chem.* 2011, 76, 3797–3804

Table 2. Effect of Reaction Solvents[a]

entry	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	hexane	72	56	33
2	toluene	72	95[d]	96
3	CH_2Cl_2	72	56	47
4	$CHCl_3$	72	76	75
5	THF	72	53	11
6	Et_2O	72	49	21
7	CH_3CN	72	22	2
8	EtOH	72	79	0
9[e]	toluene	72	94[d]	98

[a] The reactions were carried out with **1a** (0.100 mmol), **2a** (0.105 mmol), and **3h** (0.010 mmol) in solvent (1.0 mL) at room temperature. [b] Isolated yields by column chromatography. [c] Determined by chiral HPLC. [d] Isolated yields by centrifugation. [e] Catalyst **3i** was used.

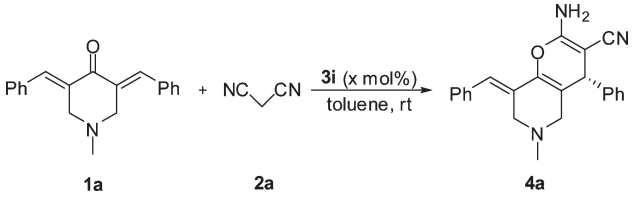
Excellent yield and good enantioselectivity could be obtained (Table 1, entry 5).[9] Quinine-derived thiourea catalyst **3e**[10] and squaric acid-derived catalyst **3f**[11] were also examined. Although excellent yields were obtained, no improvement in enantioselectivity was achieved (Table 1, entries 6−7). Further optimization was focused on the modifications of Takemoto's catalyst. In a recent study of organocatalytic conjugate addition of malonates to 3-nitro-2*H*-chromenes, we found that pyrrolidine-based catalyst **3g** provided better enantioselectivity than Takemoto's catalyst.[12] The application of **3g** in this transformation gave better yield but lower enantioselectivity (Table 1, entry 8). Further optimization of catalyst structure led to piperidine-based catalyst **3h**. To our delight, significant improvement in enantioselectivity was achieved using **3h** as the catalyst (Table 1, entry 9).

A number of reaction solvents were also examined and the results are summarized in Table 2. The effect of reaction solvent is significant. Low yield and enantioselectivity were obtained in hexane (Table 2, entry 1). Both dichloromethane and chloroform gave inferior yields and enantioselectivities (Table 2, entries 3−4). Even lower enantioselectivities were obtained in THF and ether (Table 2, entries 5−6). Polar solvent, such as ethanol and acetonitrile are incompatible for the reaction and almost racemic products were obtained (Table 2, entries 7−8). Catalyst **3i**, which is the enantiomer of **3h**, was also prepared and examined in the reaction. The enantiomeric product of **4a** was obtained in excellent yield and enantioselectivity (Table 2, entry 9).

The effect of other reaction conditions was also studied and the results are summarized in Table 3. Slightly better yield and enantioselectivity could be achieved by increasing the loading of **2a** to 1.5 equivalents (Table 3, entry 2). Further increase of the loading of **2a** did not improve the reaction performance (Table 3, entry 3). While the loadings of catalyst **3i** were decreased to 5 mol % and 2.5 mol % respectively, longer reaction time was required. The products were obtained with similar enantioselectivities (Table 3, entries 4−5). The reaction was also examined at 0 °C, but inferior yield and enantioselectivity were obtained after extended reaction time (Table 3, entry 6).

A variety of (3*E*,5*E*)-3,5-diarylmethylene-piperidin-4-ones were examined and the results are summarized in Table 4. Para substitutions of the benzene ring with methyl, methoxyl, and halogen were tolerated very well (Table 4, entries 2−6). *p*-Nitro substitution gave excellent yield, however with decreased enantioselectivity (Table 4, entry 7). *m*-Chloro and *m*-nitro substitutions led to excellent yields and good enantioselectivities

Table 3. Effect of Reaction Conditions[a]



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

entry	*x*	time (h)	yield (%)[b]	ee (%)[c]
1	10	72	94	98
2[d]	10	28	96	99
3[e]	10	12	93	98
4	5	96	89	99
5	2.5	120	85	98
6[f]	10	120	90	96

[a] The reactions were carried out with **1a** (0.100 mmol), **2a** (0.105 mmol), and **3i** in toluene (1.0 mL) at room temperature. [b] Isolated yields by centrifugation. [c] Determined by chiral HPLC. [d] **2a** (0.150 mmol) was used. [e] **2a** (0.200 mmol) was used. [f] The reaction was carried out at 0 °C.

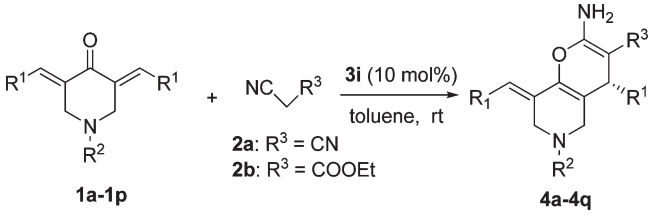
(Table 4, entries 8−9). *o*-Chloro and *o*-MeO substitution also gave excellent yields and enantioselectivities (Table 4, entries 10−11). The replacement of phenyl groups with furanyl or thiophenyl groups were also studied. The resulted dienones **1l** and **1m** showed lower reactivity and longer reaction time was necessary. **1l** provided the product **4l** in moderate yield and with good enantioselectivity (Table 4, entry 12). **1m** gave both excellent yield and enantioselectivity (Table 4, entry 13). Cinnamyl-methylene-substituted substrate **1n** provided moderate yield and enantioselectivity (Table 4, entry 14). 3,5-Dicyclohexanylene-piperidin-4-one **1o** is also applicable. Good yield and enantioselectivity could be achieved using 40 mol % **3i** after extended reaction time (Table 4, entries 15). 1-Benzyl-3,5-dibenzylidine-piperidin-4-one **1p** gave excellent yield and enantioselectivity (Table 4, entry 16). The results demonstrated that *N*-substitution of 3,5-bis(benzylidene)-4-piperidone does not exert a substantial effect on the reaction. While ethyl cyanoacetate **2b** was used, the expected product **4q** was obtained in low yield and with excellent enantioselectivity (Table 4, entry 17).

The absolute configuration of the product **4e** was assigned as *R* on the basis of the X-ray diffraction analysis.[13] The same absolute configurations are assigned for other products analogously. A number of conformationally restricted dienones **5a**−**5e** were also examined, and the results are summarized in Table 5. 4-Oxa, 4-thio, and 4-methylene substrates **5a**−**5c** provided excellent yields and good to excellent enantioselectivities (Table 5, entries 1−3). (2*E*,5*E*)-2,5-Dibenzylidenecyclopentan-one **5d** also provided excellent yield and enantioselectivity (Table 5, entry 4). However, the seven-membered ring analogue, **5e**, showed lower reactivity. Higher catalyst loading and extended reaction time were required. The product **6e** was obtained with excellent enantioselectivity but in moderate yield (Table 5, entry 5). Under the present reaction conditions, acyclic dienone **5f** provided the pyran product in only 5% yield (Table 5, entry 6); instead chiral cyclohexanone (**7**, 70% yield, 94% ee) was obtained via double conjugate addition.[4]

Furthermore, unsymmetrical dienones **8a** and **8b** were prepared and examined in the reaction (Scheme 3). In the case of **7a**,

dx.doi.org/10.1021/jo200112r |*J. Org. Chem.* 2011, 76, 3797–3804

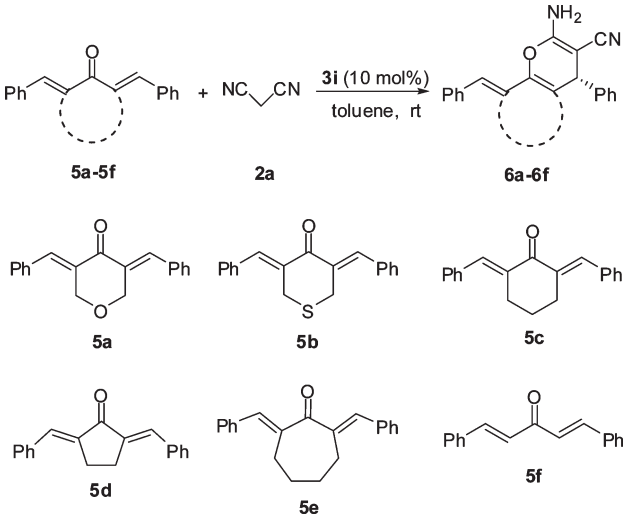
Table 4. Conjugate Addition of Malononitrile to Dienones 1a−1p.[a]



entry	R^1	R^2	time (h)	yield (%)	ee (%)[b]
1	phenyl	Me	28	**4a**, 96[c]	99
2	4-Me-phenyl	Me	42	**4b**, 98[c]	94
3	4-MeO-phenyl	Me	52	**4c**, 84[c]	94
4	4-Cl-phenyl	Me	36	**4d**, 99[d]	93
5	4-Br-phenyl	Me	28	**4e**, 95[d]	96
6	4-F-phenyl	Me	36	**4f**, 94[d]	94
7	4-NO_2-phenyl	Me	72	**4g**, 98[d]	87
8	3-Cl-phenyl	Me	30	**4 h**, 99[d]	91
9	3- NO_2-phenyl	Me	40	**4i**, 99[c]	90
10	2-Cl-phenyl	Me	38	**4j**, 99[d]	91
11	2-MeO-phenyl	Me	30	**4k**, 99[d]	97
12	furan-2-yl	Me	96	**4l**, 75[d]	92
13	thiophen-2-yl	Me	72	**4 m**, 95 [c]	97
14	*E*-styryl	Me	72	**4n**, 50[d]	77
15[e]	cyclohexanyl	Me	96	**4o**, 93[d]	83
16	phenyl	Bn	30	**4p**, 95[d]	91
17[f]	phenyl	Me	72	**4q**, 48[d]	98

[a] Reactions were carried out with **1a**−**1p** (0.10 mmol), **2a** (0.15 mmol), and **3i** (0.01 mmol) in toluene (1.0 mL) at room temperature. [b] Determined by chiral HPLC. [c] Isolated yields by centrifugation. [d] Isolated yields by flash column chromatography. [e] **3i** (0.04 mmol) was used. [f] **2b** (0.15 mmol) was used.

Table 5. Conjugate Addition of Malononitrile to Dienones 5a−5f. [a]



entry	5	time (h)	yield (%)	ee (%)[b]
1	**5a**	20	**6a**, 99[c]	95
2	**5b**	36	**6b**, 99[c]	88
3	**5c**	42	**6c**, 97[c]	92
4	**5d**	20	**6d**, 97[d]	92
5[e]	**5e**	96	**6e**, 52[d]	91
6	**5f**	6	**6f**, 5[d]	Nd[f]

[a] Reactions were carried out with **5a**−**5f** (0.10 mmol), **2a**−**2b** (0.15 mmol), and **3i** (0.01 mmol) in toluene (1.0 mL) at room temperature. [b] Determined by chiral HPLC. [c] Isolated yields by centrifugation. [d] Isolated yields by flash column chromatography. [e] **3i** (0.04 mmol) was used. [f] Not determined.

two regioisomeric pyran derivatives (**9a**/**9a′**) were obtained in excellent yield and enantioselectivities. The reaction was slightly favorable for the attack from the 4-MeO-phenyl-substituted side. Dienone **8b** with phenyl and cyclohexanyl substitutions showed lower reactivity. Two regioisomeric pyran derivatives (**9b**/**9b′**) were obtained in moderate yield after 72 h. The reaction occurred preferentially at the cyclohexanyl-substituted side and gave **9b** as the major product. Good to moderate enantioselectivities were obtained for **9b** and **9b′**, respectively.

CONCLUSIONS

In conclusion, we have developed enantioselective organocatalytic addition of malononitrile to conformationally restricted dienones. A bifunctional thiourea tertiary amine was identified as the efficient catalyst. Generally excellent enantioselectivities and yields were achieved for a variety of dienones with various substitutents and different ring sizes. The results are significantly different from the reaction of conformationally flexible dienones. The chiral pyran derivatives obtained in high enantiopurity are potential inhibitors against *M. tuberculosis*. Further studies on the other related reactions and the determination of inhibitive activity of chiral products are currently under way.

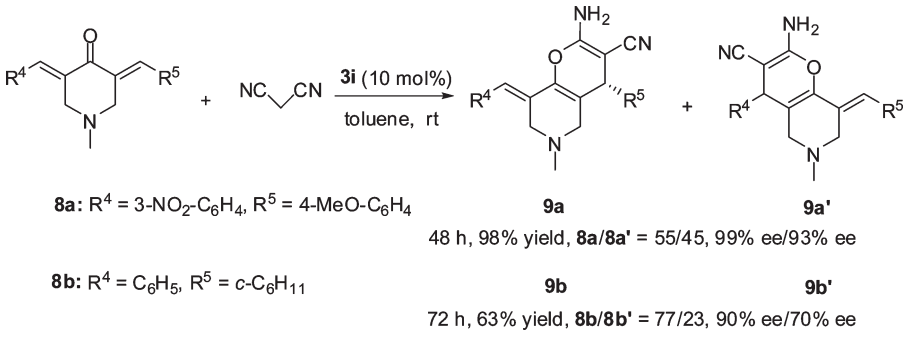
EXPERIMENTAL SECTION

General Information. All solvents were used as commercial anhydrous grade without further purification. The flash column chromatography was carried out over silica gel (230−400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a 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). High-resolution mass spectra were obtained with a LCMS-IT-TOF mass spectrometer. Infrared (IR) are represented as frequency of absorption (cm^{-1}). Enantiomeric excesses of compounds were determined by HPLC using a Daicel Chiralpak AD-H column. (3*E*,5*E*)-3,5-Bis-(arylmethylidene)-4-piperidones **1a**−**1q** and their analogues **5a**−**5f** were prepared according to the reported procedures.[6a,14] Organocatalysts **3a**,[15] **3b**,[8] **3c**,[8] **3d**,[9] **3e**,[10b] **3f**,[11] **3g**,[16] **3h**,[12] and **3i**[12] were prepared according to the literature, respectively.

General Procedure for the Synthesis of Racemic Products. A mixture of (3*E*,5*E*)-3,5-dibenzylidene-1-methylpiperidin-4-one **1a** (28.9 mg, 0.1 mmol), malononitrile **2a** (9.9 mg, 0.15 mmol), and piperidine (8.5 mg, 0.1 mmol) in ethanol (1 mL) was stirred for 30 min at room temperature. The precipitate was filtered to provide racemic **4a** as a white solid (80% yield).

dx.doi.org/10.1021/jo200112r |*J. Org. Chem.* 2011, 76, 3797–3804

Scheme 3. Reaction of Unsymmetrical Dienones



General Procedure for Organocatalytic Conjugate Addition of Malononitrile to Dienones. A mixture of (3*E*,5*E*)-3,5-dibenzylidene-1-methylpiperidin-4-one **1a** (28.9 mg, 0.1 mmol), malononitrile **2a** (9.9 mg, 0.15 mmol), and thiourea **3i** (4.5 mg, 0.01 mmol) in toluene (1 mL) was stirred for 28 h at room temperature. The white precipitate **4a** was collected by centrifugation.

(*R*,*E*)-2-Amino-8-benzylidene-6-methyl-4-phenyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4a):[6e] white solid, mp 191−194 °C. ^{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, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.83, 142.14, 140.16, 136.23, 129.15, 128.94, 128.35, 127.88, 127.62, 127.25, 126.94, 122.90, 119.67, 112.68, 60.65, 55.38, 54.70, 44.85, 41.71; MS (ESI): m/z = 356.2 $[M + H]^+$; $[\alpha]_D^{20}$ = +6.0 (c = 0.28, CH_2Cl_2); 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(major) = 7.5 min, t_r(minor) = 13.4 min.

(*R*,*E*)-2-Amino-6-methyl-8-(4-methylbenzylidene)-4-p-tolyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4b):[6a,e] white solid, mp 215 °C. ^{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, 3 H), 2.33 (s, 3 H), 2.26 (s, 3 H); MS (ESI): m/z = 384.2 $[M + H]^+$; $[\alpha]_D^{20}$ = +16.7 (c = 0.08, CH_2Cl_2); 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(major) = 6.8 min, t_r(minor) = 14.2 min.

(*R*,*E*)-2-Amino-8-(4-methoxybenzylidene)-4-(4-methoxyphenyl)-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4c):[6a,e] white solid, mp 185−187 °C. ^{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, 3 H); MS (ESI): m/z = 416.2 $[M + H]^+$; $[\alpha]_D^{20}$ = +10.2 (c = 0.09, CH_2Cl_2); 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(major) = 12.4 min, t_r(minor) = 24.0 min.

(*R*,*E*)-2-Amino-8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4d):[6e] white solid, mp 205−207 °C. ^{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, 3 H); MS (ESI): m/z = 424.1 $[M + H]^+$; $[\alpha]_D^{20}$ = +17.0 (c = 0.11, CH_2Cl_2); 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(major) = 7.6 min, t_r(minor) = 9.7 min.

(*R*,*E*)-2-Amino-8-(4-bromobenzylidene)-4-(4-bromophenyl)-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4e):[6g,17] white solid, mp 223−225 °C. ^{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, 3 H); MS (ESI): m/z = 514.0 $[M + H]^+$; $[\alpha]_D^{20}$ = +16.3 (c = 0.10, CH_2Cl_2); 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(major) = 8.2 min, t_r(minor) = 10.2 min.

(*R*,*E*)-2-Amino-8-(4-fluorobenzylidene)-4-(4-fluorophenyl)-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4f):[6e] white solid, mp 197−198 °C. ^{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, 3 H); MS (ESI): m/z = 392.2 $[M + H]^+$; $[\alpha]_D^{20}$ = +6.0 (c = 0.10, CH_2Cl_2); 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(major) = 7.5 min, t_r(minor) = 10.6 min.

(*R*,*E*)-2-Amino-6-methyl-8-(4-nitrobenzylidene)-4-(4-nitrophenyl)-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4g):[6g,17] yellow solid, mp 214−217 °C. ^{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, 3 H); MS (ESI): m/z = 446.2 $[M + H]^+$; $[\alpha]_D^{20}$ = +69.6 (c = 0.09, CH_2Cl_2); 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(major) = 19.2 min, t_r(minor) = 22.4 min.

(*S*,*E*)-2-Amino-8-(3-chlorobenzylidene)-4-(3-chlorophenyl)-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4h): white solid, mp 172−175 °C. ^{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, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.97, 144.18, 140.08, 137.91, 134.88, 134.26, 130.23, 129.63, 129.01, 128.01, 127.95, 127.38, 127.23, 126.17, 121.82, 119.36, 112.79, 59.82, 55.20, 54.45, 44.84, 41.53; IR (KBr): 3440, 3329, 2191, 1681, 1637, 1591, 1475, 1390, 1106, 787, 728, 689 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{20}Cl_2N_3O^+$ $[M + H]^+$: 424.0983, found: 424.0973; $[\alpha]_D^{20}$ = +4.7 (c = 0.09, CH_2Cl_2); 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(major) = 6.3 min, t_r(minor) = 11.9 min.

(*R*,*E*)-2-Amino-6-methyl-8-(3-nitrobenzylidene)-4-(3-nitrophenyl)-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4i):[6e] yellow solid, mp 200−202 °C. ^{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, 3 H); MS (ESI): *m*/*z* = 446.2 $[M + H]^+$; $[\alpha]_D^{20}$ = +67.4 (*c* = 0.13, CH_2Cl_2); 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(major) = 11.8 min, t_r(minor) = 28.8 min.

(*R*,*E*)-2-Amino-8-(2-chlorobenzylidene)-4-(2-chlorophenyl)-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4j):[6e] white solid, mp 208−210 °C. ^{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, 3 H); MS (ESI): *m*/*z* = 424.1 $[M + H]^+$; $[\alpha]_D^{20}$ = +9.0 (*c* = 0.12, CH_2Cl_2); 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(major) = 7.6 min, t_r(minor) = 9.7 min.

(*R*,*E*)-2-Amino-8-(2-methoxybenzylidene)-4-(2-methoxyphenyl)-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4k):[6e] white solid, mp 179−180 °C. ^{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, 3 H); MS (ESI): *m*/*z* = 416.2 $[M + H]^+$; $[\alpha]_D^{20}$ = −43.5 (*c* = 0.11, CH_2Cl_2); 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(major) = 9.0 min, t_r(minor) = 13.2 min.

(*R*,*E*)-2-Amino-4-(furan-2-yl)-8-(furan-2-ylmethylene)-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4l):[6e] white solid, mp 181−183 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 1.5 Hz, 1 H), 7.36 (d, *J* = 1.1 Hz, 1 H), 6.58 (s, 1 H), 6.44 (dd, *J* = 3.3, 1.8 Hz, 1 H), 6.34−6.32 (m, 1 H), 6.22 (d, *J* = 3.2 Hz, 1 H), 4.61 (s, 2 H), 4.20 (s, 1 H), 3.86 (d, *J* = 14.8 Hz, 1 H), 3.52 (d, *J* = 14.8 Hz, 1 H), 3.08 (d, *J* = 15.9 Hz, 1 H), 2.91 (d, *J* = 15.9 Hz, 1 H), 2.39 (s, 3 H); MS (ESI): *m*/*z* = 336.2 $[M + H]^+$; $[\alpha]_D^{20}$ = −48.8 (*c* = 0.08, CH_2Cl_2); enantiomeric excess was determined by HPLC with a CHIRALPAK AD-H column (*i*-PrOH/hexane = 20:80, 254 nm, 0.5 mL/min), t_r(major) = 18.5 min, t_r(minor) = 19.9 min.

(*S*,*E*)-2-Amino-6-methyl-4-(thiophen-2-yl)-8-(thiophen-2-ylmethylene)-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4m):[6e] white solid, mp 172−174 °C. ^{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, 3 H); MS (ESI): *m*/*z* = 368.1 $[M + H]^+$; $[\alpha]_D^{20}$ = +23.7 (*c* = 0.23, CH_2Cl_2); 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-(major) = 19.6 min, t_r(minor) = 23.6 min.

(*R*,*E*)-2-Amino-6-methyl-8-((*E*)-3-phenylallylidene)-4-styryl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4n):[6e] red solid, mp 169−181 °C. ^{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, 3 H); MS (ESI): *m*/*z* = 408.2 $[M + H]^+$; $[\alpha]_D^{20}$ = +15.4 (*c* = 0.42, CH_2Cl_2); 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) = 16.6 min.

(*R*,*E*)-2-Amino-4-cyclohexyl-8-(cyclohexylmethylene)-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4o): white solid, mp 185−188 °C. ^{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, 3 H), 2.24−2.14 (m, 1 H), 1.80−0.99 (m, 21 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.42, 141.44, 128.80, 123.55, 121.52, 110.93, 56.44, 56.31, 53.80, 45.03, 43.59, 41.34, 36.59, 33.02, 32.97, 30.53, 27.95, 26.78, 26.43, 26.30, 25.91, 25.81; IR (KBr): 3431, 3423, 2945, 2191, 1682, 1638, 1600, 1465, 1390, 1103, 1025, 908, 781, 735 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{34}N_3O^+$ $[M + H]^+$: 368.2702, found: 368.2684; $[\alpha]_D^{20}$ = +15.9 (*c* = 0.09, CH_2Cl_2); 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) = 5.3 min, t_r(minor) = 5.9 min.

(*R*,*E*)-2-Amino-6-benzyl-8-benzylidene-4-phenyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (4p):[6g,17] white solid, mp 193−194 °C. ^{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 $[M + H]^+$; $[\alpha]_D^{20}$ = −18.4 (*c* = 0.10, CH_2Cl_2); 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) = 14.9 min, t_r(minor) = 17.3 min.

(*R*,*E*)-Ethyl 2-amino-8-benzylidene-6-methyl-4-phenyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carboxylate (4q): white solid, mp 191−193 °C. ^{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), 2.41 (s, 3 H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.43, 159.71, 145.59, 139.27, 136.60, 129.15, 128.98, 128.27, 128.12, 127.40, 126.96, 126.37, 122.05, 115.89, 78.55, 59.28, 55.58, 54.62, 44.78, 41.05, 14.22; IR (KBr): 3421, 3312, 2979, 1743, 1690, 1614, 1525, 1454, 1300, 1255, 1093, 702 cm^{-1}; MS (ESI): *m*/*z* = 403.2 $[M + H]^+$; HRMS (ESI) calcd for $C_{25}H_{27}N_2O_3^+$ $[M + H]^+$: 403.2022, found: 403.2027; $[\alpha]_D^{20}$ = −26.9 (*c* = 0.13, CH_2Cl_2); 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(major) = 9.8 min, t_r(minor) = 18.5 min.

(*R*,*E*)-2-Amino-8-benzylidene-4-phenyl-4,5,7,8-tetrahydropyrano[4,3-*b*]pyran-3-carbonitrile (6a): white solid, mp 225−230 °C. ^{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), 4.61 (d, *J* = 14.2 Hz, 1 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), ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.75, 143.05, 138.09, 135.29, 128.92, 128.75, 128.53, 127.47, 127.22, 126.26, 121.35, 120.27, 113.19, 65.21, 65.00, 55.79; IR (KBr): 3430, 3335, 2191, 1682, 1640, 1621, 1596, 1489, 1453, 1393, 1362, 1158, 1101, 949, 716, 702 cm^{-1}; MS (ESI): *m*/*z* = 343.1 $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{19}N_2O_2^+$ $[M + H]^+$: 343.1447, found: 343.1431; $[\alpha]_D^{20}$ = −21.6 (*c* = 0.09, CH_2Cl_2); 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) = 11.8 min, t_r(minor) = 17.6 min.

(*S*,*Z*)-2-Amino-8-benzylidene-4-phenyl-4,5,7,8-tetrahydrothiopyrano[4,3-*b*]pyran-3-carbonitrile (6b): white solid, mp 228−230 °C. ^{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); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.65, 143.42, 141.39, 135.84, 129.13, 128.74, 128.51, 127.51, 127.39, 127.16, 126.35, 124.39, 120.23, 114.04, 55.97, 43.21, 27.20, 27.15; IR (KBr): 3428, 3331, 2190, 1682, 1640, 1621, 1596, 1489, 1453, 1393, 1361, 1158, 1101, 948, 716, 700 cm^{-1}; MS (ESI): *m*/*z* = 359.1 $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{19}N_2OS^+$ $[M + H]^+$: 359.1218, found: 359.1219; $[\alpha]_D^{20}$ = −54.7 (*c* = 0.09, CH_2Cl_2); 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) = 11.2 min, t_r(minor) = 28.5 min.

(*R*,*E*)-2-Amino-8-benzylidene-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6c):[6b,18] white solid, mp 221−224 °C. ^{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 $[M + H]^+$; $[\alpha]_D^{20}$ = −29.8 (c = 0.10, CH_2Cl_2); 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) = 9.1 min, t_r(minor) = 22.3 min.

(*R*,*E*)-2-Amino-7-benzylidene-4-phenyl-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (6d):[6b,18,19] white solid, mp 210−214 °C. ^{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 $[M + H]^+$; $[\alpha]_D^{20}$ = −25.5 (c = 0.10, CH_2Cl_2); 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) = 9.3 min, t_r(minor) = 13.6 min.

(*R*,*E*)-2-Amino-9-benzylidene-4-phenyl-4,5,6,7,8,9-hexahydrocyclohepta[*b*]pyran-3-carbonitrile (6e):[19] white solid, mp 175−179 °C. ^{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 $[M + H]^+$; $[\alpha]_D^{20}$ = −61.5 (c = 0.10, CH_2Cl_2); 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(major) = 8.4 min, t_r(minor) = 10.0 min.

***trans*-4-Oxo-2,6-diphenylcyclohexane-1,1-dicarbonitrile (7):**[4] white solid, mp 174−176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46−7.37 (m, 6 H), 7.34−7.26 (m, 4 H), 3.82 (dd, J = 7.4, 6.0 Hz, 2 H), 3.10 (qd, J = 16.8, 7.0 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.7, 135.2, 129.7, 129.3, 129.1, 113.9, 45.8, 45.1, 42.5; IR (KBr): 3453, 2191, 1642, 1596, 1410 cm^{-1}; MS (ESI): m/z = 299.1 $[M-H]^-$; HRMS (ESI) calcd for $C_{20}H_{16}N_2O^-$ $[M - H]^-$: 299.1184, found: 299.1191; $[\alpha]_D^{20}$ = +3.0 (c = 1.00, $CHCl_3$); enantiomeric excess was determined by HPLC with a CHIRALPAK IC column (*i*-PrOH/hexane = 40:60, 220 nm, 0.8 mL/min), t_r(major) = 18.1 min, t_r(minor) = 7.8 min.

(*R*,*E*)-2-amino-4-(4-methoxyphenyl)-6-methyl-8-(3-nitrobenzylidene)-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (9a): kelly green solid, mp 147−149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 − 8.11 (m, 1 H), 8.07 (s, 1 H), 7.54 (d, J = 6.1 Hz, 2H), 7.17 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.88 (s, 1 H), 4.61 (s, 2 H), 4.01 (s, 1 H), 3.81 (s, 3 H), 3.53 (d, J = 13.8 Hz, 1 H), 3.38 (d, J = 13.8 Hz, 1 H), 2.97 (d, J = 16.1 Hz, 1 H), 2.78 (d, J = 16.1 Hz, 1 H), 2.28 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.12, 158.48, 148.26, 139.44, 137.93, 134.89, 133.98, 129.58, 129.36, 128.90, 123.71, 121.95, 120.19, 119.52, 114.91, 114.37, 60.97, 55.29, 55.25, 54.45, 44.91, 40.89; IR (KBr): 3354, 2925, 2183, 1679, 1637, 1604, 1530, 1510, 1462, 1352, 1250, 1098, 824, 695 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{23}N_4O_4^+$ $[M + H]^+$: 431.1719, found: 431.1710; $[\alpha]_D^{20}$ = −19.8 (c = 0.086, CH_2Cl_2); 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(major) = 9.7 min, t_r(minor) = 16.7 min.

(*R*,*E*)-2-Amino-8-(4-methoxybenzylidene)-6-methyl-4-(3-nitrophenyl)-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (9a′): yellow solid, mp 151−153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 8.1 Hz, 1H), 8.12 (s, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.17 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 6.89 (s, 1 H), 4.69 (s, 2H), 4.17 (s, 1H), 3.83 (s, 3H), 3.59 (d, J = 13.7 Hz, 1H), 3.37 (d, J = 13.7 Hz, 1H), 2.98 (d, J = 15.8 Hz, 1H), 2.66 (d, J = 15.7 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.18, 158.99, 148.77, 144.57, 140.95, 134.12, 130.57, 129.98, 128.46, 124.85, 123.48, 122.87, 122.83, 119.14, 113.89, 110.19, 59.51, 55.29, 55.22, 54.70, 44.89, 41.65; IR (KBr): 3359, 2924, 2187, 1677, 1637, 1604, 1531, 1510, 1465, 1352, 1251, 1097, 824, 695 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{23}N_4O_4^+$ $[M + H]^+$: 431.1719, found: 431.1710; $[\alpha]_D^{20}$ = +5.4 (c = 0.20, CH_2Cl_2); enantiomeric excess was determined by HPLC with a CHIRALPAK AS-H column (*i*-PrOH/hexane = 30:70, 254 nm, 0.8 mL/min), t_r(major) = 18.5 min, t_r(minor) = 22.1 min.

■ ASSOCIATED CONTENT

Supporting Information. X-ray structural data (CIF), NMR spectra and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

Financial supports from National Natural Science Foundation of China (Nos. 20772160, 20972195), Ministry of Health of China (No. 2009ZX09501-017), and Fundamental Research Funds for the Central Universities are gratefully acknowledged.

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