Tetrahedron: *Asymmetry* 23 (2012) 461–467

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Enantioselective synthesis of 2-amino-4*H*-pyrans via the organocatalytic cascade reaction of malononitrile and α-substituted chalcones

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ARTICLE INFO

Article history:
Received 20 February 2012
Accepted 26 March 2012

ABSTRACT

An organocatalytic cascade reaction of malononitrile and α-substituted chalcones has been developed for the synthesis of chiral multisubstituted 2-amino-4*H*-pyran derivatives. A series of chiral primary/tertiary amines and cinchona alkaloids were examined as the catalysts. Quinine was found to be the most efficient catalyst in the absence of any additive. The α-substitutents of the chalcones had a siginificant effect on the yield and the enantioselectivity. A number of multisubstituted 2-amino-4*H*-pyrans were obtained in excellent yields and enantioselectivities.

1. Introduction

Over the last decade, asymmetric organocatalysis has evolved into an important tool for the synthesis of chiral compounds in addition to classical organometallic catalysis and biocatalysis.[1] The organocatalytic conjugate addition of carboanion nucleophiles to electron-deficient olefins is extremely powerful for asymmetric carbon–carbon bond formation.[2] Furthermore, cascade reactions triggered by organocatalytic conjugate additions provide highly efficient and convenient methods with which to construct cyclic chiral compounds.[3] Malononitrile is an active nucleophile with a very acidic α-proton ($pK_a = 11$). Organocatalytic conjugate additions of malononitrile to enones have also been developed.[4] Zhao et al. reported that the organocatalytic reaction of malononitrile and β,γ-unsaturated ketoesters generated 2-amino-4*H*-pyrans in good yields and enantioselectivities.[5] Wang et al. found that the organocatalytic reaction of malononitrile with (*E*)-3-benzylidenechroman-4-ones gave 2-amino-4*H*-pyrans efficiently.[6] Recently we developed an organocatalytic double conjugate addition of malononitrile to conformationally flexible dienones. Chiral cyclohexanones were obtained in excellent yields and enantioselectivities.[7] We also found that the reaction of malononitrile with conformationally restricted dienones resulted in bicyclic 2-amino-4*H*-pyrans via a cascade Michael/intramolecular cyclization sequence (Scheme 1, eq. 1).[8]

2-Amino-4*H*-pyran is an important scaffold of many natural products and bioactive compounds.[9] In addition, 2-amino-4*H*-pyrans are also used as photoactive materials.[10] New synthetic methods for making chiral 2-amino-4*H*-pyrans are highly desirable. The organocatalytic conjugate addition of malononitrile and subsequent intramolecular cyclization is an attractive strategy for their synthesis. As a continuation of our study on organocatalytic cascade reactions,[11] we are interested in the cascade reaction of malononitrile and chalcones. Such a transformation can provide chiral multisubstituted 2-amino-4*H*-pyrans for further biological evaluation. Previous studies have reported that the conjugate addition of malononitrile to chalcones provides normal adducts and the subsequent intramolecular cyclization does not occur.[4a–e] These results demonstrate that the stabilization of the enolate anion generated in the conjugate addition step is crucial for any subsequent intramolecular cyclization. We speculate that the introduction of appropriate α-substitutents can improve the stabilization of the enolate anion intermediate and allow a subsequent intramolecular cyclization. Herein we report the organocatalytic cascade reaction of malononitrile and α-substituted chalcones. Chiral multisubstituted 2-amino-4*H*-pyrans were obtained in excellent yields and enantioselectivities (Scheme 1, eq. 2).

2. Results and discussion

The reaction of α-phenyl chalcone **1a** and malononitrile **2a** was studied. Cinchona alkaloids **3a**–**3d** and organocatalysts **3e**–**3m** (Scheme 2) were examined as catalysts and the results are summarized in Table 1. Quinine **3a** catalyzed the reaction efficiently. 2-Amino-4*H*-pyran **4a** was obtained in good yield and enantioselectivity (Table 1, entry 1). Quinidine **3b**, cinchonine **3c,** and cinchonidine **3d** provided moderate to good yields and lower enantioselectivities (Table 1, entries 2–4). 6′-Demethyl quinine **3e** gave a low yield and moderate enantioselectivity (Table 1, entry 5). 6′-Demethyl-9-benzyloxy-quinine **3f** was ineffective for this reaction (Table 1, entry 6). Primary amines **3g**–**3h**, which are generally used for the activation of enones, also afforded low yields and enantioselectivities (Table 1, entries 7–8). Takemoto's amine-

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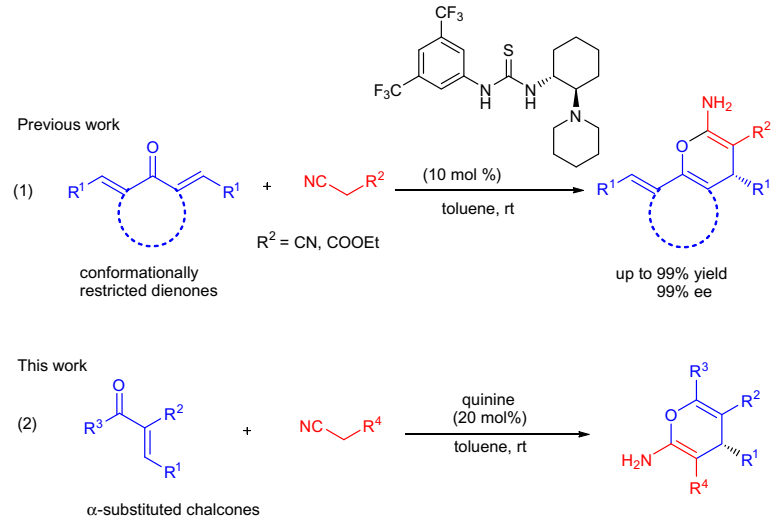
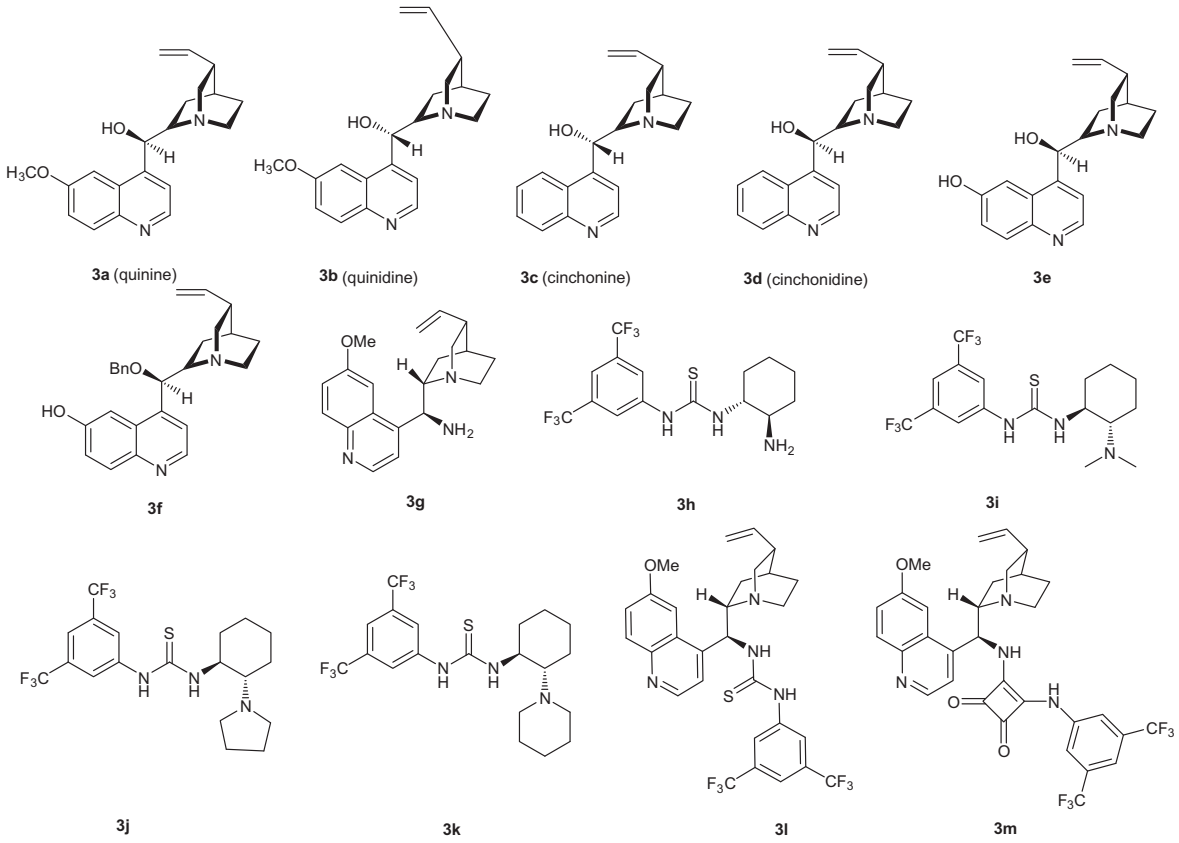
http://dx.doi.org/10.1016/j.tetasy.2012.03.018



Scheme 1. Organocatalytic cascade reaction of malononitrile and enones.



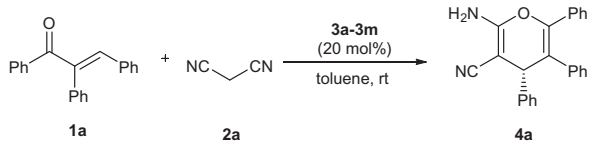
Scheme 2. Organocatalysts **3a**–**3m**.

thiourea **3i** provided low yield and enantioselectivity (Table 1, entry 9). However, improved enantioselectivities were achieved by using the more sterically demanding catalysts **3j** and **3k** (Table 1, entries 10–11). In addition, quinine-derived thiourea **3l** and squaramide **3m** gave inferior results (Table 1, entries 12–13).

The reaction solvents were screened using quinine as the catalyst and the results are summarized in Table 2. Low yield and enantioselectivity were obtained in hexane (Table 2, entry 1). The reaction provided good yield and enantioselectivity in toluene (Table 2, entry 2). Moderate yields and enantioselectivities were achieved in dichloromethane and chloroform (Table 2, entries 3–4). Low yields and enantioselectivities were observed in THF, diethyl ether, and 1,4-dioxane (Table 2, entries 5–7). Polar solvents, such as acetone and ethanol were incompatible with the reaction (Table 2, entries 8–9).

The effects of other reaction conditions were also studied and the results are summarized in Table 3. The reaction provided comparable yields and enantioselectivities in 2, 2.5, and 5 days (Table 3, entries 1–3). From these results it could be seen that the reaction actually stopped in almost 2 days. In order to improve the yield,

Table 1
Screening of catalysts **3a**–**3m**[a]

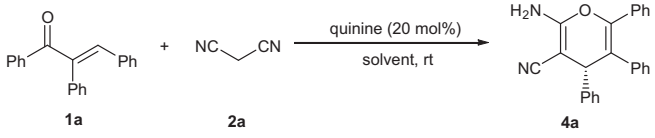


1a **2a** **4a**

Entry	Catalyst	Yield[b] (%)	Ee[c] (%)
1	**3a**	80	83
2	**3b**	85	−72
3	**3c**	31	−50
4	**3d**	74	62
5	**3e**	29	68
6	**3f**	0	n.d.[d]
7	**3g**	23	29
8	**3h**	14	−48
9	**3i**	46	49
10	**3j**	66	62
11	**3k**	50	82
12	**3l**	30	36
13	**3m**	0	n.d.[d]

[a] The reactions were carried out with **1a** (0.1 mmol), **2a** (0.15 mmol) and **3a**–**3m** (0.02 mmol) in toluene (1.0 mL) at room temperature for 2.5 days.
[b] Isolated yields after column chromatography.
[c] Ee values of purified **4a** were determined by chiral HPLC.
[d] n.d. = not determined.

Table 2
Effect of reaction solvents[a]



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

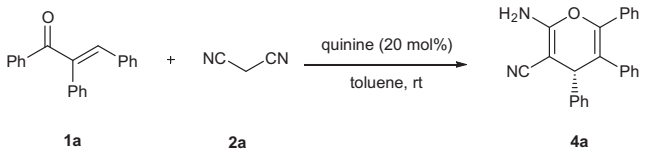
Entry	Solvent	Yield (%)	Ee (%)
1	Hexane	11	44
2	Toluene	80	83
3	CH_2Cl_2	47	75
4	$CHCl_3$	54	75
5	THF	24	44
6	Et_2O	52	51
7	1,4-Dioxane	15	47
8	Acetone	<5	n.d. [b]
9	EtOH	38	6

[a] The reactions were carried out with **1a** (0.1 mmol), **2a** (0.15 mmol) and quinine (0.02 mmol) in solvent (1.0 mL) at room temperature for 2.5 days.
[b] n.d. = not determined.

we checked the effect of the ratio of **2a**/**1a**. The reaction gave a better yield at a ratio of 2/1. Increasing the ratio further did not improve the yield (Table 3, entries 4–6). When the reaction was carried out at 0 °C, a similar enantioselectivity and lower yield were obtained after 4 days (Table 3, entry 7). When the loadings of quinine were decreased to 10 and 5 mol %, longer reaction times were required. Product **4a** was obtained with similar enantioselectivities, but in lower yields (Table 3, entries 8–9).

The substrate scope of this reaction was examined and the results are summarized in Table 4. In general, electron-withdrawing groups on the 3-phenyl group of the chalcone were tolerated very well (Table 4, entries 2–4). The reaction of 4-methoxyphenyl substituted enone **1f** gave a low yield (Table 4, entry 6). 3-Thienyl substituted enone **1g** provided the corresponding adducts with good yield and enantioselectivity (Table 4, entry 7). 3-*iso*-Propyl

Table 3
Optimization of the reaction conditions[a]



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

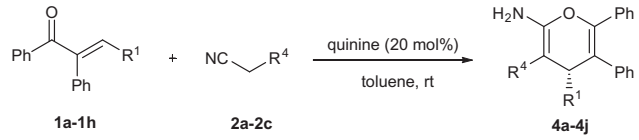
Entry	**1a** (mmol)	**2a** (mmol)	Time (days)	Yield (%)	Ee (%)
1	0.1	0.15	2	80	84
2	0.1	0.15	2.5	80	83
3	0.1	0.15	5	79	84
4	0.1	0.1	2	69	86
5	0.1	0.2	2	84	86
6	0.1	0.3	2	85	85
7[b]	0.1	0.2	4	78	85
8[c]	0.1	0.2	3	79	86
9[d]	0.1	0.2	4	72	85

[a] The reactions were carried out with **1a** (0.1 mmol), **2a** and quinine (0.02 mmol) in toluene (1.0 mL) at room temperature.
[b] The reaction was carried out at 0 °C.
[c] Quinine (0.01 mmol, 10 mol %) was used.
[d] Quinine (0.005 mmol, 5 mol %) was used.

substituted enone **1h** also gave moderate yield and good enantioselectivity (Table 4, entry 8). Ethyl cyanoacetate was also tested in the reaction, and while good enantioselectivity was obtained, the yield was poor (Table 4, entry 9). Benzoylacetonitrile was found to be unreactive for the transformation (Table 4, entry 10).

A number of 1,2-disubstituted enones **1i**–**1l** were also examined and the results are summarized in Table 5. 3,4-Diphenyl-but-3-en-2-one **1i** provided the product in good yield and enantioselectivity (Table 5, entry 1). The effect of the 2-substitutuents proved to be significant (Table 5, entries 2–4). Excellent enantioselectivity was obtained for 2-methyl chalcone **1j**, however the yield was rather low (Table 5, entry 2). Poor yield and enantioselectivity were observed for 2-ethyloxycarbonyl chalcone **1k** (Table 5, entry 3). 2-Cy-

Table 4
Conjugate addition of malononitrile to enones with various 3-substitutents[a]

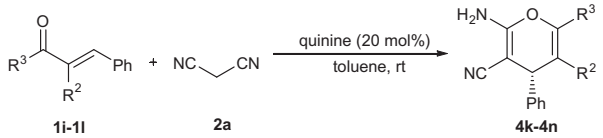


1a-1h **2a-2c** **4a-4j**

Entry	R^1	R^4	Time (h)	Yield[b] (%)	Ee[c] (%)
1	Phenyl **1a**	CN **2a**	48	**4a**, 82	86
2	4-Cl-C_6H_4 **1b**	CN **2a**	48	**4b**, 80	83
3	4-Br-C_6H_4 **1c**	CN **2a**	48	**4c**, 90	87
4	4-NO_2-C_6H_4 **1d**	CN **2a**	48	**4d**, 91	82
5	4-Me-C_6H_4 **1e**	CN **2a**	48	**4e**, 80	84
6	4-MeO-C_6H_4 **1f**	CN **2a**	72	**4f**, 37	85
7	Thienyl **1g**	CN **2a**	46	**4g**, 86	86
8	2-Propyl **1h**	CN **2a**	72	**4h**, 62	91
9[d]	Phenyl **1a**	COOEt **2b**	120	**4i**, 18	87
10	Phenyl **1a**	PhCO **2c**	168	n.r.[e]	n.d.[f]

[a] The reactions were carried out with **1** (0.1 mmol), **2** (0.2 mmol) and quinine (0.02 mmol) in toluene (1.0 mL) at room temperature.
[b] Isolated yields after column chromatography.
[c] Ee values of purified **4a**–**4i** were determined by chiral HPLC.
[d] Quinine (0.04 mmol) was used.
[e] n.r. = no reaction.
[f] n.d. = not determined.

Table 5
Conjugate addition of malononitrile to enones with various 1,2-substituents[a]



Entry	1	R^2	R^3	Time (h)	Yield[b] (%)	Ee[c] (%)
1	**1i**	Phenyl	CH_3	48	**4k**, 78	82
2[d]	**1j**	Me	Phenyl	80	**4l**, 18	95
3	**1k**	COOEt	Phenyl	24	**4m**, 12	5
4	**1l**	CN	Phenyl	4	**4n**, 97	12

[a] The reactions were carried out with **1** (0.1 mmol), **2a** (0.2 mmol) and quinine (0.02 mmol) in toluene (1.0 mL) at room temperature.
[b] Isolated yields after column chromatography.
[c] Ee values of purified **4k**–**4n** were determined by chiral HPLC.
[d] Quinine (0.04 mmol) was used.

ano chalcone **1l** provided the product in excellent yield, but with low enantioselectivity (Table 5, entry 4).

The reaction of 2-acetyl chalcone **1m** gave the product **4o** in excellent yield, but with low enantioselectivity (Scheme 3, eq. 1). In this case, enolization occurred at the acetyl group instead of the benzoyl group. Cyclic enone **1n** provided the expected 2-amino-4*H*-pyran **4p** in moderate yield and with good enantioselectivity (Scheme 3, eq. 2).

The absolute configuration of product **4g** was assigned as (*S*) on the basis of the X-ray diffraction analysis (Fig. 1).[12] Other products are suggested to have the same absolute configuration by analogy.

A bifunctional catalytic mechanism is proposed for this reaction (Scheme 4).[4e] Malononitrile is deprotonated by quinine to provide an anion. The H-bonding interaction between the hydroxy group of the quinine and the carbonyl group helps to activate the enone. In addition, an H-bonding interaction also occurs between the malononitrile anion and the ammonium group. The attack of the malononitrile anion from the *si*-face of enone gives the chiral enol anion **B**. The intramolecular cyclization of intermediate **B** and subsequent tautomerization of the imidic ester **C** provide the product **4a**.

3. Conclusions

In conclusion, we have developed an enantioselective cascade reaction of malononitrile and α-substituted chalcones. Chiral multisubstituted 2-amino-4*H*-pyrans have been prepared in good yields and enantioselectivities. Quinine was identified as the best catalyst for the reaction. The properties of the α-substitutents have a siginificant effect on the yield and the enantioselectivity. Further studies on the biological evaluation of the products are currently under way in our laboratory.

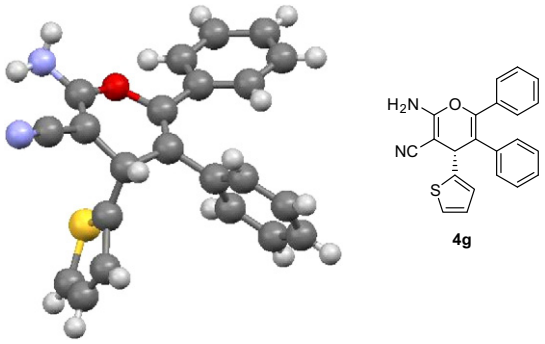
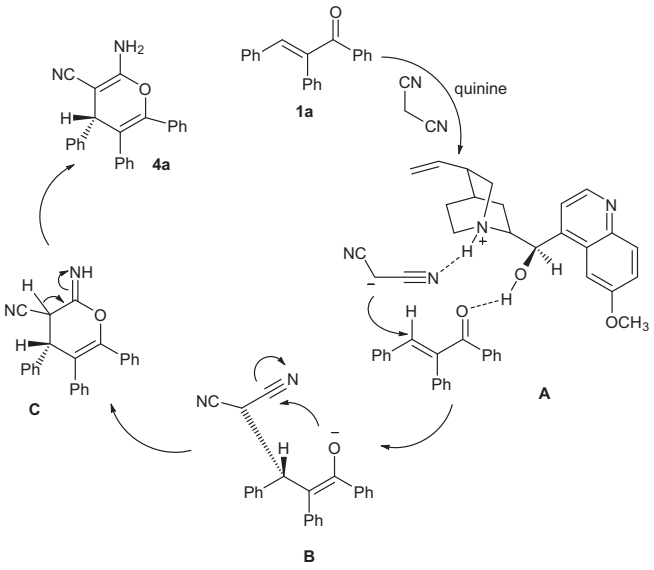


Figure 1. X-ray crystal structure of the product **4g**.

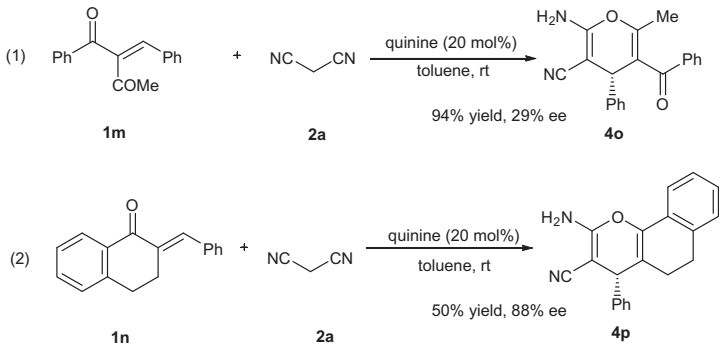


Scheme 4. Proposed catalytic mechanism.

4. Experimental

4.1. General information

All solvents were used as the commercial anhydrous grade without further purification. Flash column chromatography was carried out over silica gel (230–400 mesh). ^1H and ^{13}C NMR spectra



Scheme 3. Cascade reactions of malononitrile with enones **1m**–**1n**.

were recorded on a 400 MHz spectrometer. 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 Chiralcel OD-H column. α-Phenyl chalcones **1a**–**1h** and their analogues **1i**–**1n** were prepared according to the reported procedures.[13] Organocatalysts **3e**,[14] **3f**,[14] **3g**,[15] **3h**,[16] **3i**,[17] **3j**,[18] **3k**,[19] **3l**,[20] and **3m**[21] were prepared according to the literature.

4.2. General procedure for the organocatalytic cascade reaction of malononitrile and α-substituted chalcones

A mixture of (*E*)-1,2,3-triphenylprop-2-en-1-one **1a** (28.4 mg, 0.1 mmol), malononitrile **2a** (13.2 mg, 0.2 mmol), and quinine **3a** (6.6 mg, 0.02 mmol) in toluene (1.0 mL) was stirred for 48 h at room temperature. After the solvent was evaporated in vacuo, the residue was purified by column chromatography over silica gel (ethyl acetate:petroleum ether = 1:5) to give the product **4a**.

4.2.1. (*S*)-2-Amino-4,5,6-triphenyl-4*H*-pyran-3-carbonitrile 4a[22]

White solid, $[\alpha]_D^{20} = -99.0$ (*c* 0.098, $CHCl_3$); mp 225.2–226.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.30–7.17 (m, 10H), 7.08–7.07 (m, 3H), 6.90–6.88 (m, 2H), 6.85 (s, 2H), 4.38 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.94, 144.31, 144.10, 137.45, 133.16, 129.30, 128.91, 128.56, 128.53, 128.07, 127.86, 127.56, 126.98, 126.79, 120.26, 116.14, 57.23, 44.54; MS (ESI): *m*/*z* = 351.1 $[M+H]^+$. Enantiomeric excess was determined by HPLC with a CHIRALCEL OD-H column (*i*-PrOH/hexane = 10:90, 254 nm, 0.8 mL/min), t_R (major) = 11.8 min, t_R (minor) = 19.5 min, 86% ee.

4.2.2. (*S*)-2-Amino-4-(4-chlorophenyl)-5,6-diphenyl-4*H*-pyran-3-carbonitrile 4b[22]

White solid, $[\alpha]_D^{20} = -105.0$ (*c* 0.10, $CHCl_3$); mp 201.7–202.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.07 (m, 12H), 6.84–6.82 (m, 2H), 4.56 (s, 2H), 4.35 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.28, 144.91, 141.59, 137.09, 133.07, 132.91, 129.49, 129.26, 128.97, 128.92, 128.80, 128.34, 127.92, 127.41, 119.22, 116.37, 61.25, 44.47; MS (ESI): *m*/*z* = 385.1 $[M+H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALCEL OD-H column (*i*-PrOH/hexane = 10:90, 254 nm, 0.8 mL/min), t_R (major) = 16.0 -min, t_R (minor) = 20.1 min, 83% ee.

4.2.3. (*S*)-2-Amino-4-(4-bromophenyl)-5,6-diphenyl-4*H*-pyran-3-carbonitrile 4c

White solid, $[\alpha]_D^{20} = -117.3$ (*c* 0.104, $CHCl_3$); mp 196.9–198.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.4, 2H), 7.22–7.06 (m, 10 H), δ 6.83 (dd, *J* = 7.6, 1.4 Hz, 2H), 4.58 (s, 2H), 4.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.30, 144.93, 142.11, 137.07, 132.89, 131.86, 129.61, 129.48, 128.96, 128.80, 128.34, 127.92, 127.41, 121.20, 119.23, 116.26, 61.08, 44.53; IR (KBr): 3459, 3336, 2923, 2851, 2183, 1673, 1637, 1592, 1484, 1410, 1265, 1229, 1139, 845, 769, 696 cm^{-1}; MS (ESI): *m*/*z* = 429.0 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{18}N_2OBr^+$ $[M+H]^+$: 429.0597, found: 429.0599; Enantiomeric excess was determined by HPLC with a CHIRALCEL OD-H column (*i*-PrOH/hexane = 10:90, 254 nm, 0.8 mL/min), t_R (major) = 17.1 min, t_R (minor) = 19.6 min, 87% ee.

4.2.4. (*S*)-2-Amino-4-(4-nitrophenyl)-5,6-diphenyl-4*H*-pyran-3-carbonitrile 4d

White solid, $[\alpha]_D^{20} = -121.0$ (*c* 0.062, $CHCl_3$); mp 124.4–138.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.3, 2H), 7.37 (d, *J* = 8.3, 2H), 7.20–7.08 (m, 8H), δ 6.83 (d, *J* = 6.5, Hz, 2H), 4.69 (s, 2H), 4.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.59, 150.18, 147.20, 145.36, 136.57, 132.53, 129.36, 129.03, 128.93, 128.80, 128.54, 128.00, 127.67, 124.06, 118.90, 115.49, 61.01, 44.93; IR (KBr): 3469, 3338, 2957, 2925, 2854, 2191, 1672, 1637, 1594, 1519, 1458, 1405, 1345, 1265, 1232, 1132, 860, 768, 698 cm^{-1}; MS (ESI): *m*/*z* = 396.1 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{17}N_3NaO_3^+$ $[M + Na]^+$: 418.1162, found: 418.1186; Enantiomeric excess was determined by HPLC with a CHIRALCEL OD-H column (*i*-PrOH/hexane = 30:70, 254 nm, 0.8 mL/min), t_R (major) = 15.1 min, t_R (minor) = 11.3 min, 82% ee.

4.2.5. (*S*)-2-Amino-5,6-diphenyl-4-*p*-tolyl-4*H*-pyran-3-carbonitrile 4e[22]

White solid, $[\alpha]_D^{20} = -103.9$ (*c* 0.102, $CHCl_3$); mp 205.0–206.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.04 (m, 12H), 6.86–6.84 (m, 2H), 4.49 (s, 2H), 4.28 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.14, 144.75, 140.16, 137.54, 136.81, 133.21, 129.56, 129.46, 129.03, 128.62, 128.15, 127.87, 127.72, 127.18, 119.53, 116.84, 61.97, 44.50, 21.08; MS (ESI): *m*/*z* = 365.2 $[M+H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALCEL OD-H column (*i*-PrOH/hexane = 10:90, 254 nm, 0.8 mL/min), t_R (major) = 11.2 min, t_R (minor) = 16.4 min, 84% ee.

4.2.6. (*S*)-2-Amino-4-(4-methoxyphenyl)-5,6-diphenyl-4*H*-pyran-3-carbonitrile 4f[22]

White solid, $[\alpha]_D^{20} = -137.0$ (*c* 0.10, $CHCl_3$); mp 186.0–187.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.06 (m, 10H), 6.85–6.81 (m, 4H), 4.52 (s, 2H), 4.28 (s, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.07, 158.80, 144.57, 137.54, 135.36, 133.20, 129.58, 129.00, 128.95, 128.61, 128.17, 127.86, 127.20, 119.53, 117.01, 114.16, 62.07, 55.22, 44.19; MS (ESI): *m*/*z* = 381.1 $[M+H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALCEL OD-H column (*i*-PrOH/hexane = 10:90, 254 nm, 0.8 mL/min), t_R (major) = 17.4 min, t_R (minor) = 28.9 min, 85% ee.

4.2.7. (*S*)-2-Amino-5,6-diphenyl-4-(thiophen-2-yl)-4*H*-pyran-3-carbonitrile 4g

White solid, $[\alpha]_D^{20} = -93.3$ (*c* 0.108, $CHCl_3$); mp 196.6–199.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.10 (m, 9H), 6.95–6.93 (m, 2H), 6.87–6.85 (m, 1H), 6.79 (d, *J* = 2.8, Hz, 1H), 4.66 (s, 1H), 4.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.46, 148.02, 144.76, 137.09, 133.02, 129.57, 129.05, 128.77, 128.25, 127.91, 127.42, 126.84, 125.01, 124.93, 119.26, 116.70, 61.79, 40.01; IR (KBr): 3449, 3326, 2193, 1671, 1638, 1596, 1406, 1258, 1228, 1133, 771, 695 cm^{-1}; MS (ESI): *m*/*z* = 357.1 $[M+H]^+$; HRMS (ESI) calcd for $C_{22}H_{16}N_2NaOS^+$ $[M+Na]^+$: 379.0876, found: 379.0876; Enantiomeric excess was determined by HPLC with a CHIRALCEL OD-H column (*i*-PrOH/hexane = 10:90, 254 nm, 0.8 mL/min), t_R (major) = 14.3 min, t_R (minor) = 19.6 min, 86% ee.

4.2.8. (*S*)-2-Amino-4-isopropyl-5,6-diphenyl-4*H*-pyran-3-carbonitrile 4h

White solid, $[\alpha]_D^{20} = +69.6$ (*c* 0.056, $CHCl_3$); mp 145.0–147.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.07 (m, 10H), 4.54 (s, 2H), 3.36 (d, *J* = 2.4 Hz, 1H), 1.81–1.75 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.13, 145.46, 137.92, 133.45, 129.38, 128.72, 128.53, 128.32, 127.80, 127.24, 121.28, 118.27, 55.34, 44.92, 32.30, 20.19, 16.47; IR (KBr): 3450, 3329, 2960, 2927, 2851, 2188, 1674, 1636, 1596, 1445, 1408, 1257, 1230, 1138, 862, 749, 699 cm^{-1}; MS (ESI): *m*/*z* = 317.1 $[M+H]^+$; HRMS (ESI) calcd for $C_{21}H_{20}N_2NaO$ $[M+Na]^+$: 339.1468, found: 339.1466; Enantiomeric excess was determined by HPLC with a CHIRALCEL OD-H column (*i*-PrOH/hexane = 10:90, 254 nm, 0.8 mL/min), t_R (major) = 9.3 min, t_R (minor) = 7.3 min, 91% ee.

4.2.9. (*S*)-Ethyl 2-amino-4,5,6-triphenyl-4*H*-pyran-3-carboxylate 4i

Colorless oil. $[\alpha]_D^{20} = +22.1$ (*c* 0.068, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.16 (m, 10H), 7.09–7.07 (m, 3H), 6.85 (d, *J* = 7.4 Hz, 2H), 6.19 (br s, 2H), 4.53 (s, 1H), 4.07 (q, *J* = 6.8 Hz, 2H), 1.21 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.12, 160.07, 145.93, 144.27, 138.72, 133.63, 129.54, 128.99, 128.35, 128.29, 128.07, 128.04, 127.79, 126.86, 126.22, 119.69, 80.03, 59.38, 44.09, 14.33; IR (KBr): 3458, 3328, 2960, 2928, 2852, 1674, 1636, 1598, 1495, 1445, 1408, 1257, 1231, 1148, 862, 748, 698 cm^{-1}; MS (ESI): *m*/*z* = 398.2 $[M+H]^+$; HRMS (ESI) calcd for $C_{26}H_{24}NO_3^+$ $[M+H]^+$: 398.1751, found: 398.1757; Enantiomeric excess was determined by HPLC with a CHIRALCEL OD-H column (*i*-PrOH/hexane = 4:96, 254 nm, 0.5 mL/min), t_R (major) = 20.5 min, t_R (minor) = 18.7 min, 87% ee.

4.2.10. (*S*)-2-Amino-6-methyl-4,5-diphenyl-4*H*-pyran-3-carbonitrile 4k

White solid, $[\alpha]_D^{20} = -65.4$ (*c* 0.130, $CHCl_3$); mp 129.0–132.0 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.13 (m, 6H), 7.09–7.07 (m, 2H), 6.90–6.87 (m, 2H), 4.49 (s, 2H), 4.18 (s, 1H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.14, 142.98, 142.91, 137.51, 129.05, 128.37, 128.13, 127.87, 127.11, 126.97, 119.79, 115.05, 60.97, 44.20, 16.58; IR (KBr): 3464, 3348, 2924, 2189, 1699, 1642, 1598, 1562, 1403, 1168, 1067, 861, 795 cm^{-1}; MS (ESI): *m*/*z* = 289.1 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{17}N_2O^+$ $[M+H]^+$: 289.1355, found: 289.1345; Enantiomeric excess was determined by HPLC with a CHIRALCEL OD-H column (*i*-PrOH/hexane = 10:90, 254 nm, 0.8 mL/min), t_R (major) = 9.6 min, t_R (minor) = 14.3 min, 82% ee.

4.2.11. (*S*)-2-Amino-5-methyl-4,6-diphenyl-4*H*-pyran-3-carbonitrile 4l

Colorless oil. $[\alpha]_D^{20} = +11.6$ (*c* 0.086, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.27 (m, 10H), 4.41 (s, 2H), 3.99 (s, 1H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.38, 143.28, 142.77, 133.08, 128.80, 128.72, 128.13, 127.79, 127.31, 120.24, 110.33, 59.79, 44.38, 16.84; IR (KBr): 3462, 3344, 2928, 2196, 1698, 1646, 1596, 1459, 1405, 1168, 1068, 859, 796 cm^{-1}; MS (ESI): *m*/*z* = 289.1 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{16}N_3NaO^+$ $[M+Na]^+$: 311.1155, found: 311.1147; Enantiomeric excess was determined by HPLC with a CHIRALCEL OD-H column (*i*-PrOH/hexane = 10:90, 254 nm, 0.8 mL/min), t_R (major) = 11.4 min, t_R (minor) = 16.8 min, 95% ee.

4.2.12. (*R*)-Ethyl 6-amino-5-cyano-2,4-diphenyl-4*H*-pyran-3-carboxylate 4m[23]

White solid, $[\alpha]_D^{20} = -7.5$ (*c* 0.106, $CHCl_3$); mp 169.3–172.5 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.37 (m, 5H), 7.35–7.30 (m, 4H), 7.26–7.23 (m, 1H), 4.60 (s, 1H), 4.53 (s, 2H), 3.82 (q, *J* = 7.1 Hz, 2H), 0.80 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.81, 158.07, 154.41, 142.94, 133.17, 130.01, 128.73, 128.50, 128.07, 127.68, 127.45, 118.71, 109.79, 62.06, 60.72, 39.85, 13.36; MS (ESI): *m*/*z* = 347.1 $[M+H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALCEL AD-H column (*i*-PrOH/hexane = 10:90, 254 nm, 0.8 mL/min), t_R (major) = 12.4 min, t_R (minor) = 19.9 min, 5% ee.

4.2.13. (*S*)-2-Amino-4,6-diphenyl-4*H*-pyran-3,5-dicarbonitrile 4n[24]

White solid, $[\alpha]_D^{20} = +1.8$ (*c* 0.112, $CHCl_3$); mp 60.0–63.3 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.3 Hz, 2H), 7.57–7.32 (m, 8H), 4.82 (s, 2H), 4.35 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.80, 157.63, 140.56, 131.80, 129.82, 129.21, 128.73, 128.47, 127.78, 127.75, 117.79, 116.89, 90.88, 60.23, 40.73; MS (ESI): *m*/*z* = 300.1 $[M+H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALCEL AD-H column (*i*-PrOH/hexane = 10:90, 254 nm, 0.8 mL/min), t_R (major) = 6.2 min, t_R (minor) = 5.6 min, 12% ee.

4.2.14. (*R*)-2-Amino-5-benzoyl-6-methyl-4-phenyl-4*H*-pyran-3-carbonitrile 4o[25]

White solid, $[\alpha]_D^{20} = -54.0$ (*c* 0.100, $CHCl_3$); mp 143.2–145.9 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 7.5 Hz, 2H), 7.53–7.41 (m, 2H), 7.41–7.29 (m, 2H), 7.29–7.19 (m, 2H), 7.15 (t, *J* = 7.8 Hz, 2H), 4.62 (s, 2H), 4.59 (s, 1H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.83, 158.44, 148.71, 141.91, 137.74, 133.09, 128.73, 128.70, 128.63, 127.76, 127.45, 115.18, 60.84, 40.71, 18.04; MS (ESI): *m*/*z* = 317.1 $[M+H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALCEL AD-H column (*i*-PrOH/hexane = 10:90, 254 nm, 0.8 mL/min), t_R (major) = 14.2 min, t_R (minor) = 19.2 min, 29% ee.

4.2.15. (*S*)-2-Amino-4-phenyl-5,6-dihydro-4*H*-benzo[*h*] chromene-3-carbonitrile 4p[6]

Yellow solid, $[\alpha]_D^{20} = -44.0$ (*c* 0.092, $CHCl_3$); mp 174.0–177.9 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 6.9 Hz, 1H), 7.40–7.16 (m, 7H), 7.11 (d, *J* = 7.1 Hz, 1H), 4.55 (s, 2H), 4.08 (s, 1H), 2.86–2.63 (m, 2H), 2.22–2.14 (m, 1H), 2.10–2.02 (m, 1H); MS (ESI): *m*/*z* = 301.1 $[M+H]^+$; Enantiomeric excess was determined by HPLC with a CHIRALCEL OD-H column (*i*-PrOH/hexane = 10:90, 254 nm, 0.8 mL/min), t_R (major) = 15.5 min, t_R (minor) = 18.7 min, 88% ee.

Acknowledgements

Financial supports from the National Natural Science Foundation of China (Nos. 20972195, 21172270) and the Guangdong Engineering Research Center of Chiral Drugs are gratefully acknowledged.

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