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Enantioselective Synthesis of *N*-Phenyl-dihydropyrano[2,3-*c*]-pyrazoles via Cascade Michael Addition/Thorpe-Ziegler Type Cyclization Catalyzed by a Chiral Squaramide

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Enantioselective synthesis of biologically active dihydropyrano[2,3-*c*]pyrazoles has been achieved through a squaramide-catalysed Michael addition/Thorpe-Ziegler type cyclization cascade reaction between arylidenepyrazolones and malononitrile. A series of optically active dihydropyano[2,3-*c*]pyrazoles were obtained in excellent yields (up to 99%) and moderate to good enantioselectivities (up to 79% *ee*) under mild reaction conditions.

Keywords organocatalysis, squaramide, heterocycles, Michael addition, cyclization

Introduction

N-Phenyl-3-substituted 5-pyrazolone derivatives, which have been known since 1883, are very useful as intermediates for pharmaceuticals and are used as anti-inflammatory agents and allergy inhibitors.[1] On the other hand, due to various pharmacological properties such as anticoagulant, anticancer, antianaphylactic, and fungicidal activities, 2-amino-4*H*-pyrans or 2-amino-4*H*-chromenes are rather unusual among the pyran or chromene family members.[2] Therefore, great efforts have been devoted to synthesize pyrazolone, 2-amino pyran or 2-amino-4*H*-chromene derivatives to find more useful compounds, and significant achievements have been achieved, especially in asymmetric synthesis.[3] Pyrazolones fused to pyran rings constitute a very important class of compounds in the heterocyclic area, and were widely used as important precursors in the field of medicinal chemistry because of their useful biological and pharmacological properties such as antibacterial, anticoagulant, anticancer, spasmolytic, hypnotic, diuretic, and insecticide.[4] Consequently, it attracted us to explore a new method to construct highly functionalized chiral dihydropyrano[2,3-*c*]pyrazole derivatives through organocatalysed Michael addition/cyclization cascade reaction.

Junek *et al*. reported the first reaction for the synthesis of racemic pyrano[2,3-*c*]pyrazole derivatives from 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene in 1973.[5] Then a number of methods were developed for the synthesis of the racemic pyrano[2,3-*c*]-pyrazole derivatives.[6] In recent years, organocatalysed asymmetric reactions have made great progress,[7] which provide an easy access to the chiral pyrano[2,3-*c*]-pyrazole derivatives. In 2009, Zhao's group reported the first organocatalysed enantioselective synthesis of 6-amino-5-cyanodihydropyrano[2,3-*c*]pyrazoles from 2-pyrazolin-5-ones and benzylidenemalononitriles or multi-component reaction system using the cinchona alkaloid as the catalyst.[8a] In 2011 the same group reported the modularly designed organocatalysis model for the synthesis of 6-amino-5-cyanodihydropyrano-[2,3-*c*]pyrazoles from 3-methyl-2-pyrazolin-5-one and benzylidenemalononitriles.[8b] Since these catalytic systems were not useful for the enantioselective synthesis of *N*-phenyldihydropyrano[2,3-*c*]pyrazoles by using 2-pyrazolin-5-ones and benzylidenemalononitriles or multi-component reaction system according to our experiments, new catalytic system should be explored. Most recently, Zhao's group reported the enantioselective synthesis of fluorinated *N*-phenyl-dihydropyrano-[2,3-*c*]pyrazoles from 3-trifluoromethyl arylidene pyrazolones and malononitrile using a diaminocyclohexane-thiourea catalyst.[9] However, we are not aware of any reports about the asymmetric synthesis of *N*-phenyl-dihydropyrano[2,3-*c*]pyrazoles catalysed by squaramide. Squaramides as efficient organocatalysts have been widely used in the asymmetric catalysis.[10] Herein, we would like to present an efficient squaramide-catalysed enantioselective Michael addition/Thorpe-Ziegler type cyclization cascade reaction between arylidene pyrazolones and malononitrile. The desired *N*-phenyldihydropyrano[2,3-*c*]pyrazoles were obtained in excellent yields and moderate to good enantioselectivities, and most of the substrates were first reported by organocatalysed enantioselective synthesis.

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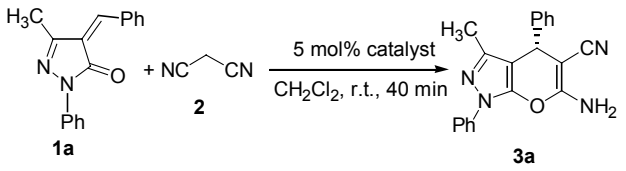
Results and Discussion

The initial investigation of the reaction between unsaturated pyrazolone **1a** and the malononitrile **2** was performed in CH_2Cl_2 at room temperature in the presence of an organocatalyst at 5 mol% loading, and the screening results are given in Table 1. The quinine-derived squaramide **I** and **II** were first screened, and the product **3a** was obtained in excellent yields with good enantioselectivities (70% *ee* and 79% *ee*) (Table 1, Entries 1 and 2). Inspired by the results, other squaramide catalysts were explored, as shown in Figure 1.

All these organocatalysts could effectively catalyze this model reaction and afforded the product **3a** in excellent yields, but the organocatalysts including quinidine-derived squaramide **III** and **IV**, chiral 1,2-diaminocyclohexane-derived squaramides **VI** and **VII**, C_2-symmetric squaramide **VIII**, *L*-phenylalanine and quinine-derived squaramide **IX**, *L*-valine and quinine-derived squaramide **X**, and one kind of thiourea bifunctional catalyst **V** afforded no better results in terms of enantioselectivity for this asymmetric reaction (Table 1, Entries 3—10). In comparison with other catalysts, quinine-derived squaramide **II** obtained a better yield and enantioselectivity, and was selected as the best catalyst for further optimization.

With the optimal catalyst established, further reaction parameters were explored. The screening of the solvents revealed that CH_2Cl_2 was still the best solvent for this reaction (Table 2, Entry 1). Compared with CH_2Cl_2, the reaction performed in $ClCH_2CH_2Cl$, $CHCl_3$, $PhCH_3$, CH_3CN, THF or Et_2O also afforded the product

Table 1 Screening of the organocatalyst[a]



Entry	Catalyst	Yield[b]/%	*ee*[c]/%
1	**I**	98	70
2	**II**	99	79
3	**III**	82	63[d]
4	**IV**	91	54[d]
5	**V**	94	39[d]
6	**VI**	98	39
7	**VII**	93	28
8	**VIII**	99	43
9	**IX**	89	18
10	**X**	98	30

[a] Reactions were carried out with **1a** (0.1 mmol) and **2** (0.15 mmol) in CH_2Cl_2 (0.5 mL) at room temperature for 40 min. [b] Isolated yield after column chromatography purification. [c] Determined by chiral HPLC analysis. [d] The opposite enantiomer.

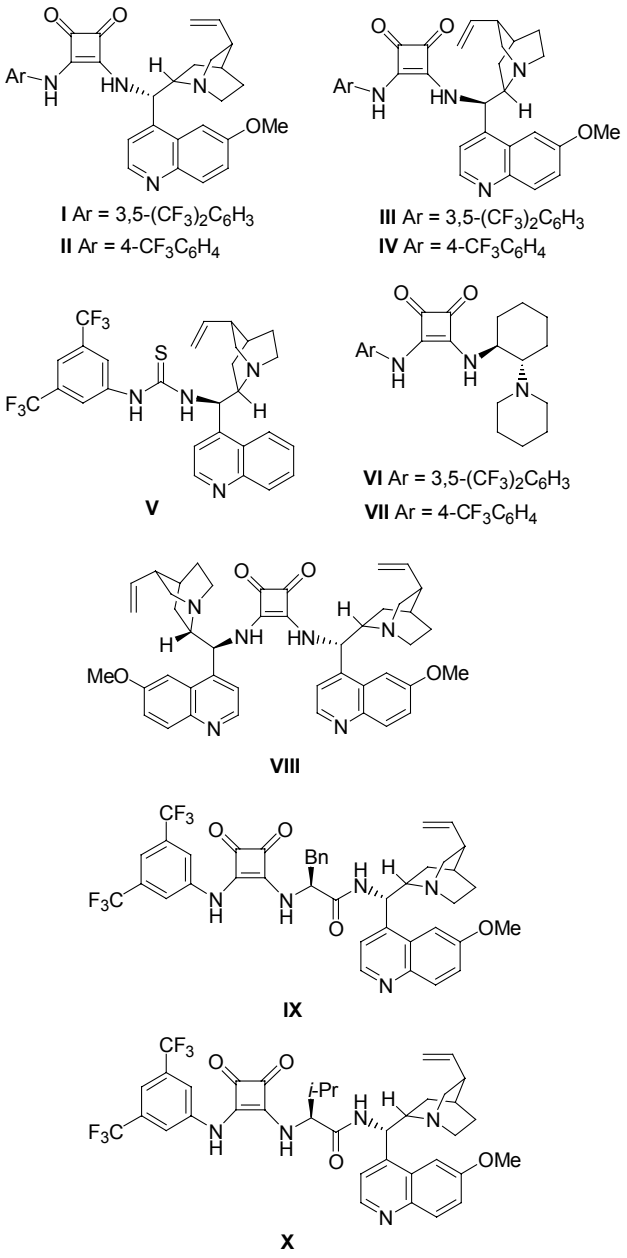
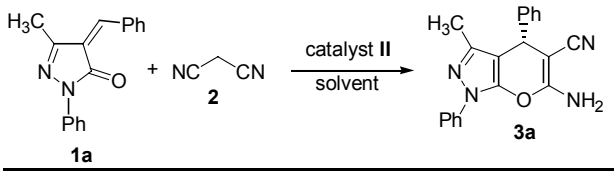


Figure 1 The structures of screened organocatalysts.

in good yields but with lower enantioselectivities (Table 2, Entries 2—5, 7 and 8). When the reaction was carried out in xylene, the similar enantioselectivity was obtained but with lower yield (Table 2, Entry 6). Using CH_2Cl_2 as the solvent, we further reduce the reaction temperature to 0 ℃ or −15 ℃, the excellent yields were still obtained but the enantioselectivities were slightly lower than that at room temperature (Table 2, Entries 9 and 10). Next, the effects of catalyst loadings and the amount of solvents were also investigated, but no better results were obtained. Consequently, the optimal reaction condition for this Michael addition/cyclization was obtained: with 5 mol% of catalyst **II** in CH_2Cl_2 at room temperature.

With the optimal reaction conditions established, a

Table 2 Optimization of reaction conditions for the enantioselective Michael addition/cyclization cascade reaction[a]



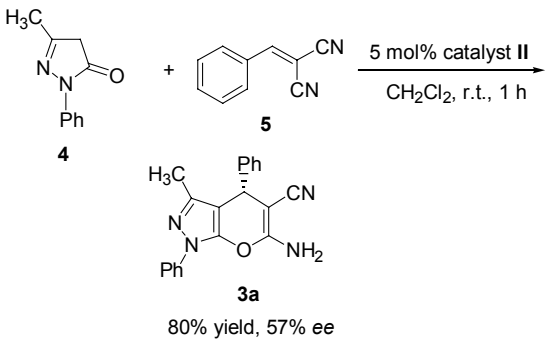
Entry	Solvent	*T*/℃	Loading/mol%	Yield[b]/%	*ee*[c]/%
1	CH_2Cl_2	r.t.	5	99	79
2	$ClCH_2CH_2Cl$	r.t.	5	98	52
3	$CHCl_3$	r.t.	5	99	58
4	$PhCH_3$	r.t.	5	83	57
5	CH_3CN	r.t.	5	72	30
6	Xylene	r.t.	5	84	77
7	THF	r.t.	5	73	63
8	Et_2O	r.t.	5	96	56
9[d]	CH_2Cl_2	0	5	99	76
10[e]	CH_2Cl_2	−15	5	96	75
11[f]	CH_2Cl_2	r.t.	2	93	63
12	CH_2Cl_2	r.t.	10	99	54
13[g]	CH_2Cl_2	r.t.	5	94	51
14[h]	CH_2Cl_2	r.t.	5	98	53

[a] Unless otherwise specified, all reactions were carried out with **1a** (0.10 mmol) and **2a** (0.15 mmol) in solvent (1.0 mL) for 40 min. [b] Isolated yield after column chromatography purification. [c] Determined by chiral HPLC analysis. [d] Reaction for 2 h. [e] Reaction for 3 h. [f] Reaction for 1 h. [g] Reaction for 80 min, and 1 mL solvent was used. [h] 0.25 mL solvent was used.

diverse array of substituted substrates was evaluated. The results are summarized in Table 3. The electronic properties of the substituent on the phenyl ring have a significant influence on the enantioselectivities. Generally, good to excellent yields were obtained with different substrates, and moderate to good enantioselectivities were obtained. Various unsaturated pyrazolones bearing either electron-withdrawing or electron-donating groups (F, Cl, Br, Me, OMe, and NO_2) on R^1 groups were investigated. The enantioselectivities of products with electron-donating group (**3b**, **3c**, **3d**, **3e**, **3f)** on the *para* position were superior to that of product with electron-withdrawing group (**3g**). However the enantioselectivity of product with electron-donating group on the *meta* position (**3k**) was better than that of any other substituted substrates. The enantioselectivities of products with *ortho* substituent (**3h**, **3i**, **3j**) were lower than those of products with *para* substituent (**3b**, **3c**, **3d**, **3e**, **3f**). In addition, the substituents on the R^2 and R^3 groups were also investigated (**3l**—**3o**), but only moderate enantioselectivities were obtained for this Michael addition/cyclization cascade system. The configurations of product **3o** was assigned according to the comparison of optical rotation with literature report,[9] and the configurations of other compounds were assigned by analogy.

Encouraged by the above results, alternative Michael addition/cyclization cascade reaction system was also explored for synthesis of dihydropyrano[2,3-*c*]pyrazoles under the optimal conditions (Scheme 1). When 3-methyl-1-phenylpyrazolin-5-one (**4**) and benzylidene malononitrile **5** were used as reactants, the product **3a** was obtained in good yield and moderate enantioselectivity.

Scheme 1 The alternative method for synthesis of **3a**



Based on the previous study on the mechanism of bifunctional squaramide-catalyzed organocatalytic Michael addition[11] and the absolute configuration of the product assigned by comparison with literature,[9] a possible transition state model is proposed and shown in Figure 2. We envision that the chiral squaramide acts as a bifunctional catalyst. The malononitrile is deprotonated by the basic nitrogen atom of the tertiary amine. Meanwhile, the arylidenepyrazolone is activated by the squaramide moiety through forming two hydrogen bonds. The deprotonated malononitrile attacks the arylidenepyrazolone from the *Si*-face to afford the *S*-configured stereocenter and the final product is formed after the following cyclization step, which is consistent with the observed results.

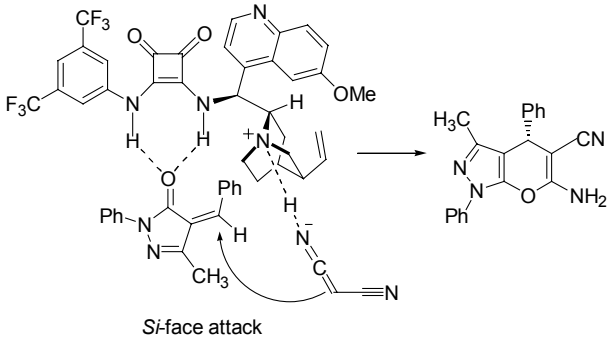


Figure 2 The proposed transition state for enantioselective Michael addition/cyclization cascade reaction.

Conclusions

In summary, we have successfully developed a squaramide-catalysed enantioselective Michael addition/cyclization cascade reaction of arylidenepyrazolone with malononitrile, and a series of potential biologically

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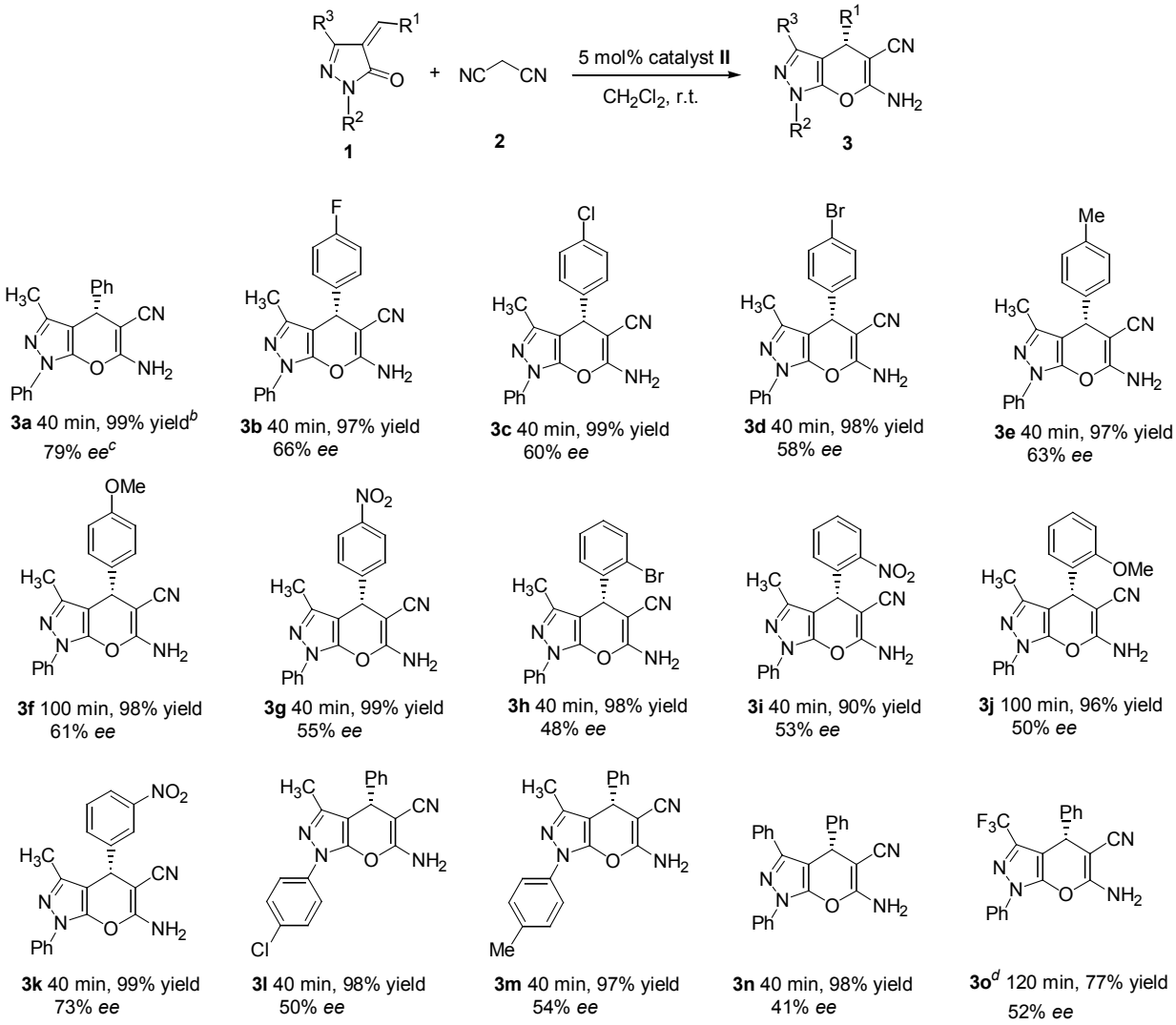
Table 3 Substrate scope of the Michael addition/cyclization cascade reaction[a]



[a] Unless noted otherwise, reactions were carried out with arylidene pyrazolone **1** (0.1 mmol), malononitrile **2** (0.15 mmol) and catalyst **II** (5 mol%) in CH_2Cl_2 (0.5 mL) at room temperature. [b] Isolated yield after column chromatography purification. [c] Determined by chiral HPLC analysis using a Daicel Chiralpak AD-H or IB column. [d] The configuration of the known product was determined according to ref. 9, the configurations of other products were assigned by analogy.

active dihydropyano[2,3-*c*]pyrazoles were first constructed by organocatalysed asymmetric synthesis. The corresponding products were obtained in excellent yields (up to 99%) and with moderate to good enantioselectivities (up to 79% *ee*) under mild reaction conditions. Further studies on chiral squaramides are underway in our group to broaden their applications in asymmetric catalysis.

Experimental

Commercially available compounds were used without further purification. Column chromatography was carried out using silica gel (200—300 mesh). Melting points were measured with an XT-4 melting point apparatus without correction. The ^{1}H NMR spectra were recorded with a Varian Mercury-plus 400 MHz or a Bruker AVIII 400 MHz spectrometer, while ^{13}C NMR spectra were recorded at 100 MHz. Infrared spectra were obtained with a Perkin Elmer Spectrum One FT-IR spectrometer. The ESI-HRMS spectra were obtained with a Bruker APEX IV FTMS spectrometer. Optical rotations were measured with a Krüss P8000 polarimeter at the indicated concentration with unit g per 100 mL. The enantiomeric excesses of the products were determined by chiral HPLC using Agilent 1200 LC instrument using Daicel Chiralpak AD-H or IB columns.

The squaramide organocatalysts were prepared following the reported procedures.[10f,10g,10l]

General procedure for the enantioselective Michael addition/cyclization reaction

To a mixture of arylidenepyrazolone **1** (0.1 mmol), and catalyst **II** (2.8 mg, 0.005 mmol) in CH_2Cl_2 (0.5 mL) was added malononitrile **2** (0.15 mmol). The mixture was vigorously stirred at room-temperature for indicated

time until the reaction was completed (monitored by TLC). The reaction mixture was then concentrated and the resulting residue was purified by silica gel column chromatography with the eluent (ethyl acetate-petroleum ether 1∶2) to afford the desired products.

(*S*)-6-Amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (3a)[6b,9] Compound **3a** was obtained according to the general procedure as a white solid (32.7 mg, 99% yield). m.p. 86－89 ℃; HPLC (Daicel Chiralpak AD-H column, *n*-hexane-isopropanol 85∶15, flow rate 1.0 mL•min^{-1}; detection at 254 nm): minor enantiomer t_R=7.1 min, major enantiomer t_R=6.1 min, 79% *ee*; $[\alpha]_D^{25}$ =–14.0 (*c*=0.62, acetone); ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.85－7.83 (m, 2H, ArH), 7.48 (t, *J*=8.0 Hz, 2H, ArH), 7.38－7.25 (m, 6H, ArH), 6.48 (s, 2H, NH_2), 4.72 (s, 1H, CH), 1.84 (s, 3H, CH_3).

(*S*)-6-Amino-4-(4-fluorophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (3b)[6j] Compound **3b** was obtained according to the general procedure as a white solid (33.7 mg, 97% yield). m.p. 164－166 ℃; HPLC (Daicel Chiralpak AD-H column; *n*-hexane-isopropanol 85∶15, flow rate 1.0 mL•min^{-1}, detection at 254 nm): minor enantiomer t_R=7.5 min, major enantiomer t_R=6.1 min, 66% *ee*; $[\alpha]_D^{25}$ =–13.2 (*c*=0.53, acetone); ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.85－7.82 (m, 2H, ArH), 7.48 (d, *J*=8.0 Hz, 2H, ArH), 7.40－7.36 (m, 2H, ArH), 7.31 (t, *J*=7.4 Hz, 1H, ArH), 7.13 (t, *J*=8.8 Hz, 2H, ArH), 6.51 (s, 2H, NH_2), 4.76 (s, 1H, CH), 1.85 (s, 3H, CH_3).

(*S*)-6-Amino-4-(4-chlorophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (3c)[6b] Compound **3c** was obtained according to the general procedure as a white solid (36.1 mg, 99% yield). m.p. 160－164 ℃; HPLC (Daicel Chiralpak AD-H column, *n*-hexane-isopropanol 85∶15, flow rate 1.0 mL•min^{-1}, detection at 254 nm): minor enantiomer t_R=7.6 min, major enantiomer t_R=6.1 min, 60% *ee*; $[\alpha]_D^{25}$ =–28.4 (*c*=0.53, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.80－7.77 (m, 2H, ArH), 7.50 (t, *J*=8.0 Hz, 2H, ArH), 7.41 (d, *J*=8.4 Hz, 2H, ArH), 7.35－7.29 (m, 3H, ArH), 7.27 (s, 2H, NH_2), 4.73 (s, 1H, CH), 1.80 (s, 3H, CH_3).

(*S*)-6-Amino-4-(4-bromophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (3d)[6b] Compound **3d** was obtained according to the general procedure as a white solid (40.0 mg, 98% yield). m.p. 173－177 ℃; HPLC (Daicel Chiralpak AD-H column, *n*-hexane-isopropanol 85∶15, flow rate 1.0 mL•min^{-1}, detection at 254 nm): minor enantiomer t_R=7.8 min, major enantiomer t_R=6.2 min, 58% *ee*; $[\alpha]_D^{25}$ =–25.4 (*c*=0.52, acetone); ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.79 (d, *J*=8.0 Hz, 2H, ArH), 7.55 (d, *J*=8.0 Hz, 2H, ArH), 7.50 (t, *J*=8.0 Hz, 2H, ArH), 7.32 (t, *J*=7.4 Hz, 1H, ArH), 7.27－7.23 (m, 4H, ArH＋NH_2), 4.72 (s, 1H, CH), 1.80 (s, 3H, CH_3).

(*S*)-6-Amino-3-methyl-1-phenyl-4-(*p*-tolyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (3e)[6j] Compound **3e** was obtained according to the general procedure as a white solid (33.1 mg, 97% yield). m.p. 145－148 ℃; HPLC (Daicel Chiralpak AD-H column, *n*-hexane-isopropanol 85∶15, flow rate 1.0 mL•min^{-1}, detection at 254 nm): minor enantiomer t_R=6.7 min, major enantiomer t_R=5.5 min, 63% *ee*; $[\alpha]_D^{25}$ =–26.7 (*c*=0.42, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.79 (dd, J_1=1.2 Hz, J_2=8.8 Hz, 2H, ArH), 7.49 (t, *J*=8.0 Hz, 2H, ArH), 7.32 (t, *J*=7.4 Hz, 1H, ArH), 7.18－7.12 (m, 6H, ArH＋NH_2), 4.63 (s, 1H, CH), 2.29 (s, 3H, CH_3), 1.79 (s, 3H, CH_3).

(*S*)-6-Amino-4-(4-methoxyphenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (3f)[6b] Compound **3f** was obtained according to the general procedure as a white solid (35.0 mg, 98% yield). m.p. 159－162 ℃; HPLC (Daicel Chiralpak AD-H column, *n*-hexane-isopropanol 85∶15, flow rate 1.0 mL•min^{-1}, detection at 254 nm): minor enantiomer t_R=9.2 min, major enantiomer t_R=7.2 min, 61% *ee*; $[\alpha]_D^{25}$ =＋9.9 (*c*=0.42, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.79－7.76 (dd, J_1=1.0 Hz, J_2=8.6 Hz, 2H, ArH), 7.50 (t, *J*=8.0 Hz, 2H, ArH), 7.34－7.30 (m, 1H, ArH), 7.18－7.16 (m, 4H, ArH＋NH_2), 6.90 (d, *J*=8.8 Hz, 2H, ArH), 4.63 (s, 1H, CH), 3.75 (s, 3H, OCH_3), 1.79 (s, 3H, CH_3).

(*S*)-6-Amino-3-methyl-4-(4-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (3g)[6j] Compound **3g** was obtained according to the general procedure as a white solid (37.0 mg, 99% yield). m.p. 177－181 ℃; HPLC (Daicel Chiralpak AD-H column, *n*-hexane-isopropanol 85∶15, flow rate 1.0 mL•min^{-1}, detection at 254 nm): minor enantiomer t_R=14.7 min, major enantiomer t_R=10.5 min, 55% *ee*; $[\alpha]_D^{25}$ =–18.0 (*c*=0.49, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.24 (d, *J*=8.8 Hz, 2H, ArH), 7.80 (d, *J*=7.6 Hz, 2H, ArH), 7.59 (d, *J*=8.8 Hz, 2H, ArH), 7.51 (t, *J*=8.0 Hz, ArH), 7.38 (s, 2H, NH_2), 7.34 (t, *J*=7.4 Hz, ArH), 4.93 (s, 1H, CH), 1.80 (s, 3H, CH_3).

(*S*)-6-Amino-4-(2-bromophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (3h)[12] Compound **3h** was obtained according to the general procedure as a white solid (39.9 mg, 98% yield). m.p. 139－142 ℃; HPLC (Daicel Chiralpak AD-H column, *n*-hexane-isopropanol 85∶15, flow rate 1.0 mL•min^{-1}, detection at 254 nm): minor enantiomer t_R=7.0 min, major enantiomer t_R=6.4 min, 48% *ee*; $[\alpha]_D^{25}$ =–23.8 (*c*=0.63, acetone); ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.84－7.81 (m, 2H, ArH), 7.62 (d, *J*=8.8 Hz, 1H, ArH), 7.49－7.44 (m, 2H, ArH), 7.37－7.28 (m, 3H, ArH), 7.23－7.18 (m, 1H, ArH), 6.58 (s, 2H, NH_2), 5.27 (s, 1H, CH), 1.82 (s, 3H, CH_3).

(*S*)-6-Amino-3-methyl-4-(2-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (3i)[6l] Compound **3i** was obtained according to the general procedure as a white solid (33.5 mg, 90% yield). m.p. 152－155 ℃; HPLC (Daicel Chiralpak IB column, *n*-hexane-isopropanol 85∶15, flow rate 1.0 mL•min^{-1}, detection at 254 nm): minor enantiomer t_R=13.9 min,

major enantiomer t_R = 16.8 min, 53% *ee*; $[\alpha]_D^{25}$ = + 15.3 (*c* = 1.7, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.90 (dd, J_1=1.0 Hz, J_2=8.2 Hz, 1H, ArH), 7.80 (dd, J_1=1.0 Hz, J_2=8.6 Hz, 2H, ArH), 7.70 (dt, J_1=1.2 Hz, J_2=7.6 Hz, 1H, ArH), 7.56−7.49 (m, 4H, ArH), 7.38 (s, 2H, NH_2), 7.36−7.32 (m, 1H, ArH), 5.21 (s, 1H, CH), 1.76 (s, 3H, CH_3).

(*S*)-6-Amino-4-(2-methoxyphenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (3j)[6l] Compound **3j** was obtained according to the general procedure as white solid (34.3 mg, 96% yield). m.p. 87−90 ℃; HPLC (Daicel Chiralpak IB column, *n*-hexane–isopropanol 85∶15, flow rate 1.0 mL•min^{-1}, detection at 254 nm): minor enantiomer t_R= 8.6 min, major enantiomer t_R=9.6 min, 50% *ee*; $[\alpha]_D^{25}$ =–28.1 (*c*=1.7, acetone); ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.84−7.81 (m, 2H, ArH), 7.49−7.44 (m, 2H, ArH), 7.31−7.22 (m, 2H, ArH), 7.16 (dd, J_1=1.6 Hz, J_2=7.6 Hz, 1H, ArH), 7.03 (dd, J_1=0.8 Hz, J_2= 8.4 Hz, 1H, ArH), 6.93 (dt, J_1=0.8 Hz, J_2=7.4 Hz, 1H, ArH), 6.40 (s, 1H, NH_2), 5.15 (s, 1H, CH), 3.87 (s, 3H, OCH_3), 1.85 (s, 3H, CH_3).

(*S*)-6-Amino-3-methyl-4-(3-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (3k)[6e] Compound **3k** was obtained according to the general procedure as a white solid (37.1 mg, 99% yield). m.p. 183−186 ℃; HPLC (Daicel Chiralpak AD-H column, *n*-hexane-isopropanol 85∶15, flow rate 1.0 mL min^{-1}, detection at 254 nm): minor enantiomer t_R=13.5 min, major enantiomer t_R=9.9 min, 73% *ee*; $[\alpha]_D^{25}$ =–12.8 (*c*=0.53, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.18−8.15 (m, 2H, ArH), 7.82−7.78 (m, 3H, ArH), 7.70−7.66 (m, 1H, ArH), 7.51 (t, *J*=8.0 Hz, 2H, ArH), 7.39 (s, 2H, NH_2), 7.36−7.32 (m, 1H, ArH), 4.98 (s, 1H, CH), 1.81 (s, 3H, CH_3).

(*S*)-6-Amino-1-(4-chlorophenyl)-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (3l) Compound **3l** was obtained according to the general procedure as a white solid (36 mg, 98% yield). m.p. 178−181 ℃; HPLC (Daicel Chiralpak IB column, *n*-hexan-isopropanol 85∶15, flow rate 1.0 mL•min^{-1}, detection at 254 nm): minor enantiomer t_R=8.1 min, major enantiomer t_R=9.5 min, 50% *ee*; $[\alpha]_D^{25}$ =–21.9 (*c*=0.54, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.83 (d, *J*=9.2 Hz, 2H, ArH), 7.53 (d, *J*=8.8 Hz, 2H, ArH), 7.35 (t, *J*=7.6 Hz, 2H, ArH), 7.28−7.24 (m, 5H, ArH+NH_2), 4.68 (s, 1H, CH), 1.78 (s, 3H, CH_3); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 159.2, 145.6, 143.8, 143.4, 136.3, 130.1, 129.1, 128.4, 127.7, 127.0, 121.3, 119.8, 98.8, 58.1, 36.6, 12.5; IR (KBr) *v*: 3469, 3360, 3323, 3195, 2922, 2198, 2189, 1659, 1588, 1514, 1489, 1458, 1411, 1381, 1264, 1177, 1129, 1095, 1061, 1011, 828, 754, 701, 659, 522, 507 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{16}ClN_4O$ $[M + H]^+$ 363.10072, found 363.10142.

(*S*)-6-Amino-3-methyl-4-phenyl-1-(*p*-tolyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (3m)[6k] Compound **3m** was obtained according to the general procedure as a white solid (33.9 mg, 97% yield). m.p. 174−177 ℃; HPLC (Daicel Chiralpak IB column, *n*-hexane-isopropanol 85∶15, flow rate 0.5 mL•min^{-1}, detection at 254 nm): minor enantiomer t_R=13.5 min, major enantiomer t_R=14.2 min, 54% *ee*; $[\alpha]_D^{25}$ =–20.2 (*c*=0.53, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.66 (d, *J*=8.4 Hz, 2H, ArH), 7.35 (t, *J*=7.6 Hz, 2H, ArH), 7.29 (d, *J*=8.4 Hz, 2H, ArH), 7.25 (d, *J*=8.0 Hz, 3H, ArH), 7.19 (s, 2H, NH_2), 4.67 (s, 1H, CH), 2.35 (s, 3H, CH_3), 1.77 (s, 3H, CH_3).

(*S*)-6-Amino-1,3,4-triphenyl-1,4-dihydropyrano-[2,3-*c*]pyrazole-5-carbonitrile (3n)[6m] Compound **3n** was obtained according to the general procedure as a white solid (38.3 mg, 98% yield). m.p. 159−163 ℃; HPLC (Daicel Chiralpak AD-H column, *n*-hexane-isopropanol 85∶15, flow rate 1.0 mL•min^{-1}, detection at 254 nm): minor enantiomer t_R=6.9 min, major enantiomer t_R=8.6 min, 41% *ee*; $[\alpha]_D^{25}$ =+43.0 (*c*=0.53, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.95−7.93 (m, 2H, ArH), 7.63−7.55 (m, 4H, ArH), 7.43−7.39 (m, 1H, ArH), 7.30−7.21 (m, 9H, ArH+NH_2), 7.16−7.12 (m, 1H, ArH), 5.10 (s, 1H, CH).

(*S*)-6-Amino-1,4-diphenyl-3-(trifluoromethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (3o) Compound **3o** was obtained according to the general procedure as a white solid (29.4 mg, 77% yield). m.p. 170−173 ℃; HPLC (Daicel Chiralpak IB column, *n*-hexane-isopropanol 85∶15, flow rate 1.0 mL•min^{-1}, detection at 254 nm): minor enantiomer t_R=9.0 min, major enantiomer t_R=12.7 min, 52% *ee*; $[\alpha]_D^{25}$ =+4.8 (*c*=1.45, CH_2Cl_2); ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.91−7.88 (m, 2H, ArH), 7.60−7.56 (m, 2H, ArH), 7.50−7.45 (m, 1H, ArH), 7.36−7.30 (m, 4H, ArH), 7.29−7.24 (m, 1H, ArH), 6.61 (s, 0.3H, NH_2), 4.85 (s, 1H, CH). Lit.[9] (*R*)-enantiomer: m.p. 185−187 ℃; $[\alpha]_D^{25}$ =–12.3 (*c*=1.39 in CH_2Cl_2), 80% *ee*.

The reaction of 3-methyl-1-phenyl-2-pyrazolin-5-one with 2-benzylidenemalononitrile for synthesis of 3a

To a mixture of 3-methyl-1-phenyl-2-pyrazolin-5-one **4** (17.4 mg, 0.1 mmol), and catalyst **II** (2.8 mg, 0.005 mmol) in CH_2Cl_2 (0.5 mL) was added 2-benzylidenemalononitrile **5** (18.5 mg, 0.12 mmol). The mixture was vigorously stirred at room temperature for 1 h. The reaction mixture was then concentrated and the resulting residue was purified by silica gel column chromatography with the eluent (ethyl acetate-petroleum ether 1∶2) to afford the desired product **3a** (26.4 mg, 80% yield).

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