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Organocatalyzed asymmetric tandem Michael-cyclization reaction of 4-benzylidene-3-methylpyrazol-5-ones and malononitrile: Stereocontrolled construction of pyrano[2,3-c]pyrazole scaffold

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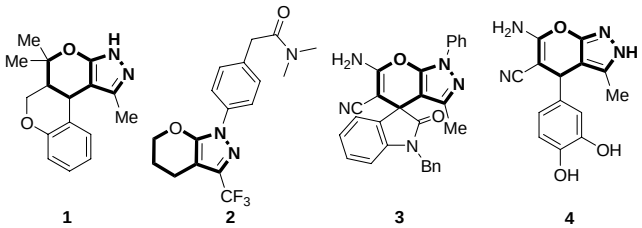
An efficient approach for the stereocontrolled construction of pyrano[2,3-c]pyrazole scaffold has been developed. Under the catalysis of a bifunctional squaramide derived from (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine, the asymmetric tandem Michael addition/cyclization reaction of 4-benzylidenepyrazol-5(4*H*)-ones and malononitrile proceeded efficiently to furnish the desired pyrano[2,3-c]pyrazoles in satisfactory yields with high levels of enantioselectivity (up to 99% ee).

Introduction

Pyrazole, a five-membered heterocycle containing two adjacent nitrogen atoms, is a core motif found in a number of small molecules that possess a wide range of bioactivities such as anticancer,[1] antibacterial,[2] antiparasitic,[3] antiviral,[4] analgesics,[5] antiglycemic,[6] anti-inflammatory,[7] antiobesity,[8] insecticidal agents,[9] PPI inhibitors,[10] B-Raf kinase inhibitors,[11] MAO inhibitors[12] and LPA1 antagonists.[13] Owing to the interesting applications of pyrazoles in the field of drug discovery and agricultural research, the fusion of such parent molecules to form polycyclic systems, which adds functional diversity, is increasingly becoming a fruitful area of the study for their biological activity. Among such fused heterocycles, pyrano[2,3-c]pyrazoles play an essential role in biologically active compounds and therefore represent an interesting template for medicinal chemistry. Currently, several functionally substituted pyrano[2,3-c]pyrazole derivatives have been found to have a broad range of bioactive properties. For example, tetrahydropyrano[2,3-c]pyrazoles **1**, **2** are serve as fungicide[14] and AMPA receptor activity enhancer,[15] respectively. Spiro-dihydropyrano[2,3-c]pyrazole **3** is found to be a new class of potential antioxidants.[16] Compound **4** is identified as a potential inhibitor of human Chk1 kinase.[17] Consequently, the considerable biological activities of pyrano[2,3-*c*]pyrazoles have stimulated considerable research directed for synthesis of derivatives of this ring system. As a result, the construction of pyrano[2,3-*c*]pyrazole scaffold has been elegantly established through different modes of reaction and cyclization: two-component, three-component and four-component reactions.[18] Nevertheless, to the best of our knowledge, there are only two reports of performing the reaction in an enantioselective fashion. In 2009, Zhao reported the first enantioselective synthesis of 2,4-dihydropyrano[2,3-*c*]pyrazoles through cupreine catalyzed reaction of 3-methyl-2-pyrazolin-5-one and benzylidenemalononitriles, but the enantioselectivities obtained were substantially lower for most cases.[19] Enders realized the synthesis of 1,4,5,6-tetrahydropyrano[2,3-c]pyrazoles with high enantioselectivities via a secondary amine catalyzed asymmetric Michael/Wittig/oxa-Michael reaction sequence.[20] Therefore, the development of alternative highly efficient synthesis of pyrano[2,3-c]pyrazole derivatives with high levels of enantioselectivity will be of great importance and remains a challenge task. As part of our ongoing studies on organocatalyzed asymmetric Michael addition initiated tandem reaction,[21] in 2013, we developed a chiral squaramide catalyzed tandem Michael addition-cyclization reaction of 4-benzylidenepyrazol-5(4*H*)-ones and malononitrile, which afford an efficient access to the stereocontrolled construction of 1,4-dihydropyrano[2,3-c]pyrazole scaffold. The preliminary results of this work have already been communicated.[22] Herein, the full details of the scope and limitations and the mechanistic insights of this organocatalytic, asymmetric tandem Michael addition-cyclization reaction are described.



1 2 3 4

Figure 1. Bioactive pyrano[2,3-*c*]pyrazoles.

Results and discussion

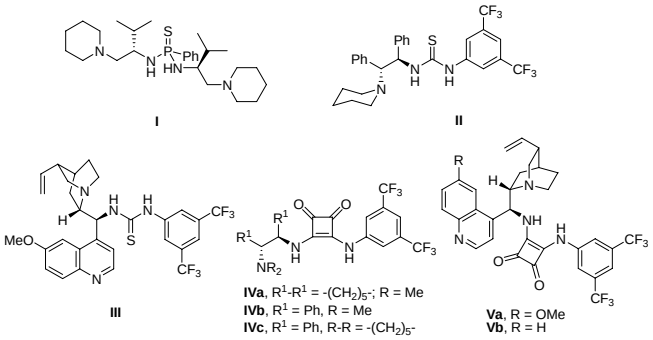
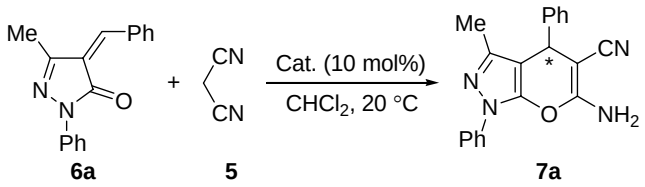


Figure 2. Screened bidentate hydrogen bond donor catalysts.

We started our investigations by choosing the reaction of malononitrile (**5**) and 4-benzylidene-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**6a**) as the model. Several readily available bifunctional bidentate hydrogen bond donor catalysts (Figure 2) were screened as the catalysts. The results are summarized in Table 1.

Table 1. Catalyst evaluation [a]

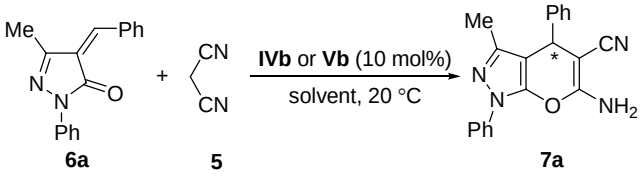


Entry	Catalyst	Time (h)	Yield (%) [b]	Ee (%) [c]
1	**I**	3	81	–2
2	**II**	3	89	8
3	**III**	3	81	–11
4	**IVa**	6	92	63
5	**IVb**	8	99	83
6	**IVc**	22	84	53
7	**Va**	2.5	76	–39
8	**Vb**	3	95	–84

a. All reactions were carried out with **5** (0.12 mmol), **6a** (0.10 mmol), and the catalyst (10 mol%) in methylene chloride (1 mL) at 20 °C. b. Yield of the isolated product after column chromatography on silica gel. C. Determined by HPLC analysis using a chiral stationary phase.

On the basis of the previous successful experience in the use of chiral bifunctional thiophosphonodiamides, which are effective promoters for activation of nitroolefins for Michael addition,[23] we initially employed thiophosphonodiamide **I** as the catalyst for the model reaction. Indeed, the process proceeded smoothly to give Michael-cyclization product **7a** in high yield albeit with quite low enantioselectivity (entry 1). Then we probed thiourea[24] and squaramide-based catalysts[25] for this cascade reaction under the same reaction conditions. When thiourea **II** and **III** were used as the catalysts, no improvement on enantioselectivity was observed at all (entries 2 and 3). In sharp contrast, when squaramide-based catalysts were used as the catalysts, product **7a** was obtained in high yields with markedly improved ee values (entries 4–8, 39–84%). These results suggest that the reaction is very sensitive to the type of catalyst and the subtle changes in the catalyst structure. Among the screened squaramide catalysts, (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine derived catalyst **IVb** and cinchonidine-based catalyst **Vb** were found to be the most promising catalyst candidates for the reaction, affording the desired product with enantioselectivities of 83% ee and 84% ee, respectively (entries 5 and 8). So we chose these two catalysts for further evaluation of the solvent and temperature effect on the reaction, respectively. The results are collected in Table 2.

Table 2. Optimization of reaction conditions [a]



Entry	Solvent	Time (h) [b]	Yield (%) [b,c]	Ee (%) [b,d]
1	CH_2Cl_2	16 (3)	>99 (95)	83 (–84)
2	$CHCl_3$	16 (2)	87 (>99)	82 (–82)
3	THF	72 (5)	89 (>99)	29 (–83)
4	CH_3CN	72 (4.5)	92 (>99)	48 (–32)
5	EA	72 (13)	67 (85)	77 (–74)
6	$PhCH_3$	20 (1)	85 (76)	19 (–14)
7 [e]	CH_2Cl_2	27 (8)	81 (91)	91 (–72)
10 [f]	CH_2Cl_2	72 (27)	55 (76)	97 (–88)

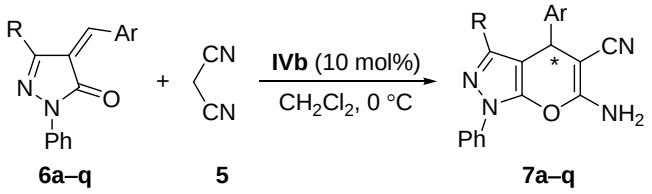
a. Unless specified otherwise, all reactions were carried out with **5** (0.12 mmol), **6a** (0.10 mmol), and catalyst **IVb** or **Vb** (10 mol%) in 1 mL of solvent at 20 °C. b. Data in parentheses were obtained in the presence of catalyst **Vb**. c. Yield of the isolated product after column chromatography on silica gel. d. Determined by HPLC analysis using a chiral stationary phase. e. The reaction was performed at 0 ºC. f. The reaction was carried out at –20 ºC.

Solvent evaluation revealed that methylene chloride was still the best solvent for the selected two catalysts. No superior results were obtained by performing the reaction in other commonly used solvents such as chloroform, THF, acetonitrile, ethyl acetate and toluene (entries 2–6 vs entry 1). Further investigation demonstrated that the reaction temperature had different effect on the reaction for the two catalysts. For catalyst **IVb**, it was gratifying that variation in temperature resulted in significant improvement on enantioselectivity of the reaction. When the reaction was performed at 0 ºC, the corresponding adduct was obtained with an increased ee value

of 91% (entry 7). An even higher enantioselectivity of 97% ee was achieved by conducting the reaction at –20 ºC at the expense of reaction time and yield (entry 8). Nevertheless, in the case of catalyst **Vb**, either performing the reaction at 0 or –20 ºC led to no obvious enhancement of stereocontrol for the reaction. Therefore, catalyst **IVb** was chosen as the favorable catalyst for this cascade Michael-cyclization process and the optimal reaction temperature is 0 ºC with respect to both the enantioselectivity and yield.

To test the substrate scope of the cascade Michael addition-cyclization reaction, the reaction of various unsaturated pyrazolones **6** and malononitrile **5** was studied under the optimized conditions (10 mol % of bifunctional squaramide **IVb** as the catalyst, in CH_2Cl_2 at 0 ºC). The results are summarized in Table 3.

Table 3. **IVb**-catalyzed tandem Michael addition/cyclization reaction of 4-benzylidenepyrazol-5-onse (**6**) and malononitrile (**5**) [a]



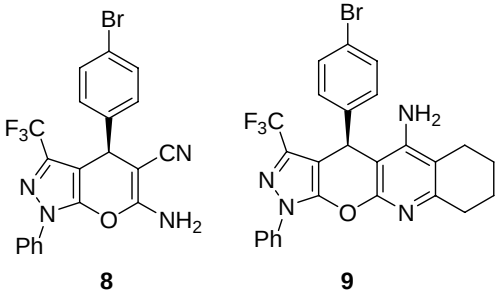
6a–q **5** **7a–q**

Entry	**7** (R, Ar)	Time (h)	Yield (%) [b]	Ee (%) [c]
1	**7a** (Me, Ph)	27	81	91
2	**7b** (Me, 4-FC_6H_4)	38	>99	97
3	**7c** (Me, 4-ClC_6H_4)	19	92	99
4	**7d** (Me, 2,4-$Cl_2C_6H_3$)	30	93	75
5	**7e** (Me, 3-ClC_6H_4)	24	>99	81
6	**7f** (Me, 2-ClC_6H_4)	36	>99	85
7	**7g** (Me, 4-BrC_6H_4)	47	90	95
8	**7h** (Me, 3-BrC_6H_4)	32	95	81
9	**7i** (Me, 2-BrC_6H_4)	40	>99	85
10	**7j** (Me, 4-$CF_3C_6H_4$)	38	80	79
11	**7k** (Me, 3-$CF_3C_6H_4$)	21	95	84
12	**7l** (Me, 3-$O_2NC_6H_4$)	21	92	71
13	**7m** (Me, 4-$MeOC_6H_4$)	96	64	93
14	**7n** (Me, 2-$MeOC_6H_4$)	168	69	74
15	**7o** (Me, 4-MeC_6H_4)	47	94	95
16	**7p** (Me, 2-Thienyl)	84	85	96
17	**7q** (Pr, Ph)	51	91	86

a. All reactions were carried out with **5** (0.12 mmol), **6a** (0.10 mmol), and catalyst **IVb** (10 mol%) in 1 mL of methylene chloride at 0 °C. b. Yield of the isolated product after column chromatography on silica gel. c. Determined by HPLC analysis using a chiral stationary phase.

As shown in Table 3, the newly developed cascade process was applicable to a wide range of 4-benzylidene substituted pyrazol-5-ones (**6**), delivering the corresponding 1,4-dihydropyrano[2,3-c]pyrazoles (**7**) with good to exellent yields. With respect to the enantioselectivity, the substitution pattern have an obvious impact on the stereochemical outcome of the reaction. Except for the *para*-trifluoromethyl substituted substrate **6j** (entry 10, 79% ee), generally, the intruduction of either electron-donating or electron-withdrawing group at the *para*-position of the phenyl ring is favourable for the stereocontrol of the reaction, affording the desired products with excellent enantioselectivities (entries 2, 3, 7, 13 and 14, 93–99% ee). However, the reactions of *ortho*-, *meta*- or multisubstituted 4-benzylidenepyrazol-5-ones all proceeded with considerably decreased ee values (ranged from 71% to 85%). These results hint that the enantioselectivity of this reaction is most likely governed by not only electronic factors but also steric factors. Moreover, electron-rich 2-furyl substituted substrate **6p** was also proved to be a suitable reaction partner with malononitrile, furnishing the addition-cyclization product 7p in 85% yield with 96% ee (entry 16). In addition, replacing the methyl group in 3-methyl-4-benzylidenepyrazol-5-one (**6a**) with a larger propyl group (**6q**) also leads to a slightly droped ee value of the product **7q** (86% ee vs 91% ee, entries 1 and 17).

Several attempts to determine the absolute configuration of 1,4-dihydropyrano[2,3-c]pyrazole derivatives **7** via the X-ray crystallographic analysis are failed. In all cases, it gives the data for the racemic compound, in which both enantiomers are present in equal quantities in a well-defined arrangement within the crystal lattice. Over the course of continuing effort to assign the absolute configuration of the product, Zhao and coauthors reported the enantioselective synthesis of functionalized fluorinated dihydropyrano[2,3-c]pyrazoles catalyzed by a bifunctional thiourea. The absolute configuration of **8** was assigned as *S* by X-ray crystallography analysis of its derivative **9** (Figure 3).[26]

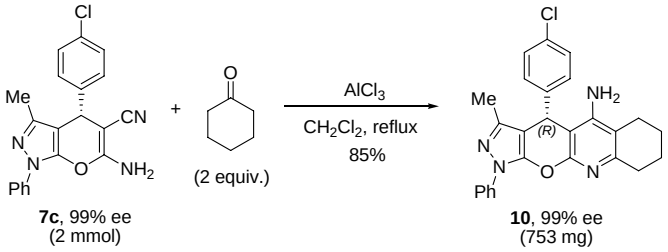


8 **9**

Figure 3. Trifluoromethyl substituted dihydropyrano[2,3-c]pyrazoles.

Similarly, the crystalline derivative **10** of 1,4-dihydropyrano[2,3-c]pyrazole **7c** was obtained in good yield (85%) without any loss of stereochemical integrity (99% ee) (Scheme 1). The absolute configuration of compound **10** is unequivocally established as *R* by X-ray analysis (Figure 4).

Since none of the bonds to the stereogenic carbon have been broken during the Friedländer reaction, the original configuration of compound **7c** is retained. Therefore, the absolute configuration of addduct **7c** obtained by squaramide **IVb**-catalyzed tandem Michael-cyclization reaction between 4-benzylidenepyrazol-5-onse (**6**) and malononitrile (**5**) was assigned as *R*, and the stereochemistry of the other 1,4-dihydropyrano[2,3-c]pyrazoles **7** could be tentatively assigned by assuming an analogous enantioinduction (Figure 5).



Scheme 1. Synthesis of the crystaline drivative **10**.

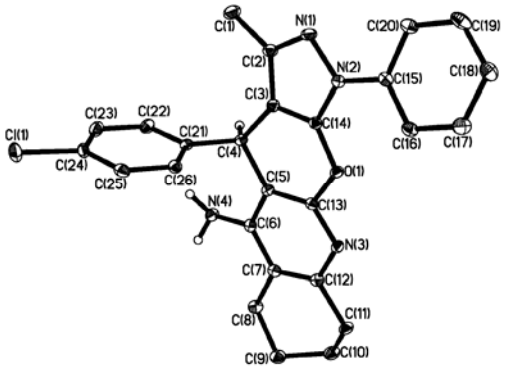


Figure 4. X-ray crystal structure of (*R*)-**10**. Most of the hydrogen atoms and uncoordinated solvent have beenomitted for clarity.

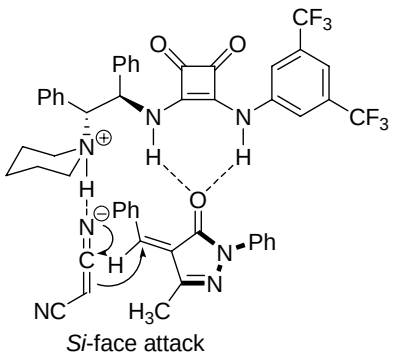


Figure 5. Proposed ternary complex that explain the stereochemistry associated with the initial Michael addition.

Experimental

General Methods: All reagents and solvents were commercial grade and purified prior to use when necessary. NMR spectra were acquired on Varian 400 MHz instrumental. Chemical shifts are measured relative t residual solvent peaks as an internal standard set to δ 7.26 and δ 77.0 ($CDCl_3$), 2.50 and 38.45 (DMSO-d_6), 2.05 and 206.26 (Acetone-d_6). Specific rotations were measured on a Perkin-Elmer 341MC polarimeter. Enantiomeric excesses were determined on a Shimadzu LC-20A instrument (chiral column; mobile phase: Hexane/*i*-PrOH). HRMS was performed on a Varian QFT-ESI instrumental. Melting points were determined on a Taike X-4 melting point apparatus. All temperatures were uncorrected.

General procedure for IVb–catalyzed asymmetric tandem Michael addition/cyclization reaction of 4-benzylidenepyrazol-5-ones and malononitrile: Squaramide catalyst **IVb** (11.8 mg, 0.02 mmol) and 4-benzylidenepyrazol-5-ones **6** (0.20 mmol) was dissolved in methylene chloride (1 mL) and the resulting solution was stirred at 20 °C for 0.5 h. Then malononitrile **6** (0.24 mmol) was added in one portion, and the resulting mixture was stirred at the same temperatu until the completion of the reaction (Monitored by TLC). After removal of the solvent under reduced pressure the crude product was purified by column chromatography on silica gel (200–300 mesh, PE/EtOAc = 20/1) to afford the desired pyrano[2,3-c]pyrazoles **7**. The title compounds were fully characterized by ^{1}H, ^{13}C NMR, HRMS and specific rotation data.

(*R*)-6-amino-1,4-dihydro-3-methyl-1,4-diphenylpyrano[2,3-c]pyrazole-5-carbonitrile (**7a)**: White solid, m.p. 161–163 °C, 81% yield, $[\alpha]_D^{25}$ –10.4 (c 0.5, $CHCl_3$), 91% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.89 (s, 3 H), 4.65 (s, 1 H), 4.72 (br. s, 2 H), 7.24–7.37 (m, 6 H), 7.45 (t, *J* = 8.0 Hz, 2 H), 7.65 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 12.9, 37.4, 63.7, 98.4, 119.2, 121.2, 126.8, 127.6, 127.9, 128.8, 129.3, 137.6, 142.0, 143.8, 146.4, 158.2. HRMS (ESI) m/z calc'd for $C_{20}H_{15}N_4O$ $[M–H]^-$: 327.1251, found 327.1256. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 5.00 (minor) and 5.96 min (major).

(*R)*-6-amino-4-(4-fluorophenyl)-1,4-dihydro-3-methyl-1-phenyl-pyrano[2,3-c]pyrazole-5-carbonitrile (**7b**): White solid, m.p. 154–156 °C, 99% yield, $[\alpha]_D^{25}$ –16.4 (c 0.5, $CHCl_3$), 97% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.89 (s, 3 H), 4.65 (s, 1 H), 4.77 (s, 2 H), 7.04 (t, *J* = 8.0 Hz, 2 H), 7.21–7.24 (m, 2 H), 7.31 (t, *J* = 7.2 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.64 (d, J = 7.6 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 12.9, 36.7, 63.5, 98.1, 115.7 (d, *J* = 21.6 Hz), 119.0, 121.2, 126.8, 129.3, 129.4 (d, *J* = 8.3 Hz), 137.4, 137.9 (d, *J* = 3.1 Hz), 143.7, 146.3, 158.2, 162.1 (d, *J* = 246.1 Hz). HRMS (ESI) m/z calc'd for $C_{20}H_{14}FN_4O$ $[M–H]^-$: 345.1157, found 345.1152. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 4.90 (minor) and 6.19 min (major).

(*R*)-6-Amino-4-(4-chlorophenyl)-1,4-dihydro-3-methyl-1-phenyl-pyrano[2,3-c]pyrazole-5-carbonitrile (**7c**): White solid, m.p. 154–156 °C, 92% yield, $[\alpha]_D^{25}$ –19.6 (c 0.5, $CHCl_3$), 99% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.89 (s, 3 H), 4.65 (s, 1 H), 4.76 (br. s, 2 H), 7.19 (d, *J* = 7.6 Hz, 2 H), 7.33 (d, *J* = 7.6 H 3 H), 7.46 (t, *J* = 7.2 Hz, 2 H), 7.64 (d, *J* = 7.6 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 12.9, 36.9, 63.2, 97.9, 118.9, 121.2, 126.9, 129.0, 129.2, 129.3, 133.4, 137.4, 140.6, 143.8, 146.2, 158.2. HRMS (ESI) m/z calc'd for $C_{20}H_{14}ClN_4O$ $[M–H]^-$: 361.0861, found 361.0859. HPLC analysis (Chiralpak AD-H

column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 4.92 (minor) and 6.32 min (major).

(*R*)-6-Amino-4-(3-chlorophenyl)-1,4-dihydro-3-methyl-1-phenyl-pyrano[2,3-c]pyrazole-5-carbonitrile (**7d**): White solid, m.p. 152–153 °C, 99% yield, $[\alpha]_D^{25}$ –0.8 (c 0.5, $CHCl_3$), 82% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.90 (s, 3 H), 4.63 (s, 1 H), 4.85 (br. s, 2 H), 7.16 (d, *J* = 6.8 Hz, 1 H), 7.20 (s, 1 H), 7.26–7.33 (m, 2 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.64 (d, *J* = 7.6 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 12.9, 37.1, 62.7, 97.7, 118.9, 121.2, 126.2, 126.8, 127.8, 127.9, 129.3, 130.0, 134.7, 137.3, 143.7, 144.1, 146.2, 158.4. HRMS (ESI) m/z calc'd for $C_{20}H_{14}ClN_4O$ $[M–H]^–$: 361.0861, found 361.0864. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 4.83 (minor) and 5.58 min (major).

(*R*)-6-Amino-4-(2-chlorophenyl)-1,4-dihydro-3-methyl-1-phenyl-pyrano[2,3-c]pyrazole-5-carbonitrile (**7e**): White solid, m.p. 151–152 ºC, >99% yield, $[\alpha]_D^{25}$ –6.4 (c 0.5, $CHCl_3$), 85% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87 (s, 3 H), 4.91 (s, 2 H), 5.27 (s, 1 H), 7.18–7.26 (m, 3 H), 7.30 (t, *J* = 7.6 Hz, 1 H), 7.38 (d, *J* = 7.6 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 7.64 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ12.6, 33.8, 61.8, 98.0, 118.9, 121.1, 126.7, 127.5, 128.7, 129.2, 129.8, 130.5, 133.2, 137.4, 139.1, 143.9, 146.1, 158.9. HRMS (ESI) m/z calc'd for $C_{20}H_{16}ClN_4O$ $[M+H]^+$: 363.1007, found 363.1011. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 6.17 (minor) and 6.92 min (major).

(*R*)-6-amino-4-(2,4-dichlorophenyl)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (**7f**): White solid, m.p. 176–177 °C, 93% yield, $[\alpha]_D^{25}$ –17.6 (c 0.5, $CHCl_3$), 75% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.90 (s, 3 H), 4.78 (s, 2 H), 5.26 (s, 1 H), 7.15 (s, 1 H), 7.24 (s, 1 H), 7.33 (s, 1 H), 7.43–7.47 (m, 3 H), 7.63 (s, 2 H). ^{13}C NMR (100.6 MHz, DMSO-d_6): 12.2, 33.5, 56.1, 97.2, 119.4, 119.9, 126.2, 128.0, 128.8, 129.2, 132.4, 133.0, 137.3, 139.1, 144.2, 144.7, 159.8. HRMS (ESI) m/z calc'd for $C_{20}H_{15}Cl_2N_4O_2$ $[M+H]^+$: 397.0617, found 397.0620. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 4.75 (minor) and 5.56 min (major).

(*R*)-6-Amino-4-(4-bromophenyl)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (**7g**): White solid, m.p. 164–166 °C, 90% yield, $[\alpha]_D^{25}$ +6.4 (c 0.5, $CHCl_3$), 95% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.89 (s, 3 H), 4.64 (s, 1 H), 4.72 (br. s, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 7.2 Hz, 1 H), 7.44–7.49 (m, 4 H), 7.64 (d, *J* = 7.6 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 12.9, 37.0, 63.3, 97.8, 118.8, 121.2, 121.6, 126.9, 129.3, 129.6, 132.0, 137.4, 141.1, 143.8, 146.2, 158.2. HRMS (ESI) m/z calc'd for $C_{20}H_{14}BrN_4O$ $[M–H]^–$: 405.0356, found 405.0354. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 5.01 (minor) and 6.33 min (major).

(*R*)-6-Amino-4-(3-bromophenyl)-1,4-dihydro-3-methyl-1-phenyl-pyrano[2,3-c]pyrazole-5-carbonitrile (**7h**): White solid, m.p. 157–159 °C, 95% yield, $[\alpha]_D^{25}$ +2.0 (c 0.5, $CHCl_3$), 81% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.90 (s, 3 H), 4.61 (s, 1 H), 4.87 (br. s, 2 H), 7.21–7.26 (m, 2 H), 7.31 (t, *J* = 7.2 Hz, 1 H), 7.35 (s, 1 H), 7.40–7.47 (m, 3 H), 7.64 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 12.9, 37.1, 62.6, 97.7, 118.9, 121.2, 123.0, 126.6, 126.8, 129.2, 130.3, 130.7, 130.8, 137.4, 143.7, 144.4, 146.1, 158.2. HRMS (ESI) m/z calc'd for $C_{20}H_{14}BrN_4O$ $[M–H]^–$: 405.0356, found 405.0358. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): Rt = 4.95 (minor) and 5.75 min (major).

(*R*)-6-Amino-4-(2-bromophenyl)-1,4-dihydro-3-methyl-1-phenyl-pyrano[2,3-c]pyrazole-5-carbonitrile (**7i**): White solid, m.p. 163–165 °C, 99% yield, $[\alpha]_D^{25}$ –2.8 (c 0.5, $CHCl_3$), 85% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.87 (s, 3 H), 4.90 (br. s, 2 H), 5.28 (s, 1 H), 7.11–7.18 (m, 2 H), 7.28 (t, *J* = 7.2 Hz, 2 H), 7.43 (t, *J* = 7.2 Hz, 2 H), 7.57 (d, *J* = 7.6 Hz, 1 H), 7.63 (d, *J* = 6.8 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 12.7, 36.4, 62.0, 98.1, 118.8, 121.1, 123.5, 126.7, 128.1, 129.0, 129.2, 130.8, 133.1, 137.4, 140.8, 143.9, 146.1, 158.8. HRMS (ESI) m/z calc'd for $C_{20}H_{14}BrN_4O$ $[M–H]^–$: 405.0356, found 405.0354. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 6.32 (minor) and 6.95 min (major).

(*R*)-6-Amino-4-(4-trifluoromethylphenyl)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (**7j**): White solid, m.p. 163–165 °C, 80% yield, $[\alpha]_D^{25}$ –3.7 (c 0.5, $CHCl_3$), 79% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.89 (s, 3 H), 4.74 (s, 1 H), 4.80 (br. s, 2 H), 7.33 (t, *J* = 7.2 Hz, 1 H), 7.38 (d, *J* = 7.6 Hz, 2 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.64 (t, *J* = 8.4 Hz, 4 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 12.9, 37.3, 62.7, 97.7, 118.8, 121.2, 124.0 (q, *J* = 272.1 Hz), 125.9 (q, *J* = 3.7 Hz), 127.0, 128.3, 129.3, 129.9 (q, *J* = 32.5 Hz), 137.4, 143.8, 146.0, 146.1, 158.5. HRMS (ESI) m/z calc'd for $C_{21}H_{16}F_3N_4O$ $[M+H]^+$: 397.1271, found 397.1273. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 4.38 (minor) and 5.17 min (major).

(*R*)-6-Amino-4-(3-(trifluoromethyl)phenyl)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (**7k**): White solid, m.p. 151–153 °C, 95% yield, $[\alpha]_D^{25}$ –4.4 (c 0.5, $CHCl_3$), 84% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.86 (s, 3 H), 4.72 (s, 1 H), 4.96 (br. s, 2 H), 7.31 (t, *J* = 7.2 Hz, 1 H), 7.42–7.49 (m, 5 H), 7.54 (s, 1 H), 7.64 (d, *J* = 7.6 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 12.8, 37.3, 62.2, 97.5, 118.8, 121.1, 123.9 (q, *J* = 272.3 Hz), 124.5, 126.8, 129.2, 129.3, 131.1 (q, *J* = 32.4 Hz), 131.4, 137.3, 143.1, 143.8, 146.0, 158.6. HRMS (ESI) m/z calc'd for $C_{21}H_{16}F_3N_4O$ $[M+H]^+$: 397.1271, found 397.1275. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 4.42 (minor) and 5.11 min (major).

(*R*)-6-Amino-1,4-dihydro-3-methyl-4-(3-nitrophenyl)-1-phenyl-pyrano[2,3-c]pyrazole-5-carbonitrile (**7l**): White solid, m.p. 184–187 °C, 92% yield, $[\alpha]_D^{25}$ –4.0 (c 0.25, CHCl3), 71% ee. ^{1}H NMR (400 MHz, DMSO-d_6): 1.80 (s, 3 H), 4.97 (s, 1 H), 7.33 (t, *J* = 7.2 Hz, 1 H), 7.36 (s, 2 H), 7.50 (t, *J* = 7.6 Hz, 2 H), 7.67 (d, *J* = 8.0 Hz, 1 H), 7.79 (d, *J* = 7.6 Hz, 3 H), 8.15 (s, 2 H) ^{13}C NMR (100.6 MHz, DMSO-d_6): 12.5, 36.1, 57.0, 97.5, 119.7, 120.0, 122.1, 122.2, 126.2, 129.2, 130.2, 134.6, 137.3, 143.9, 145.0, 145.9, 147.9, 159.6. HRMS (ESI) m/z calc'd for $C_{20}H_{16}N_5O_3$ $[M+H]^+$: 374.1248, found 374.1244. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 7.25 (minor) and 9.80 min (major).

(*R*)-6-Amino-1,4-dihydro-4-(4-methoxyphenyl)-3-methyl-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (**7m**): White solid, m.p. 171–172 °C, 94% yield, $[\alpha]_D^{25}$ –3.2 (c 0.5, $CHCl_3$), 95% ee. ^{1}H NMR (400 MHz, DMSO-d_6): 1.78 (s, 3 H), 3.74 (s, 3 H), 4.62 (s, 1 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 7.16 (br. s, 2 H), 7.17 (d, *J* = 8.4 Hz, 2 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.78 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (100.6 MHz, DMSO-d_6): 12.5, 35.9, 54.9, 58.5, 98.8, 113.7, 119.8, 120.0, 126.5, 128.7, 129.2, 135.5, 137.5, 143.7, 145.2, 158.1, 159.2. HRMS

(ESI) m/z calc'd for $C_{21}H_{19}N_4O_2$ $[M+H]^+$: 359.1503, found 359.1505. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 5.61 (minor) and 7.11 min (major).

(*R*)-6-Amino-1,4-dihydro-4-(2-methoxyphenyl)-3-methyl-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (**7n**): White solid, m.p. 131–133 °C, 69% yield, $[\alpha]_D^{25}$ –4.0 (c 0.5, $CHCl_3$), 74% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.90 (s, 3 H), 3.86 (s, 3 H), 4.71 (br. s, 2 H), 5.19 (s, 1 H), 6.91 (d, *J* = 7.2 Hz, 2 H), 7.06 (d, *J* = 7.2 Hz, 1 H), 7.23 (t, *J* = 7.6 Hz, 1 H), 7.30 (d, *J* = 7.6 Hz, 1 H), 7.44 (t, *J* = 7.2 Hz, 2 H), 7.65 (d, *J* = 7.6 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 12.6, 29.9, 55.5, 63.0, 98.5, 111.0, 119.4, 121.0, 126.5, 128.5, 129.1, 129.2, 130.1, 137.6, 144.2, 146.2, 156.9, 158.8. HRMS (ESI) m/z calc'd for $C_{21}H_{18}N_4NaO_2$ $[M+Na]^+$: 381.1322, found 381.1325. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 6.97 (minor) and 7.81 min (major).

(*R*)-6-Amino-1,4-dihydro-3-methyl-1-phenyl-4-p-tolylpyrano[2,3-c]pyrazole-5-carbonitrile (**7o**): White solid, m.p. 171–172 °C, 94% yield, $[\alpha]_D^{25}$ –3.2 (c 0.5, $CHCl_3$), 95% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.89 (s, 3 H), 2.33 (s, 3 H), 4.61 (s, 1 H), 4.74 (br. s, 2 H), 7.14 (br. s, 4 H), 7.30 (t, *J* = 6.4 Hz, 1 H), 7.44 (d, *J* = 7.2 Hz, 2 H), 7.65 (d, *J* = 7.2 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 12.9, 21.1, 37.0, 64.0, 98.5, 119.1, 121.1, 126.7, 127.7, 129.2, 129.5, 137.1, 137.6, 139.0, 143.8, 146.4, 158.1. HRMS (ESI) m/z calc'd for $C_{21}H_{17}N_4O$ $[M-H]^-$: 341.1408, found 341.1409. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 4.56 (minor) and 5.56 min (major).

(*S*)-6-Amino-1,4-dihydro-3-methyl-1-phenyl-4-(thiophen-2-yl)pyrano[2,3-c]pyrazole-5-carbonitrile (**7p**): White solid, m.p. 165–166 °C, 85% yield, $[\alpha]_D^{25}$ –35.6 (c 0.5, $CHCl_3$), 96% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.97 (s, 3 H), 4.67 (s, 2 H), 4.96 (s, 1 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 7.20 (s, 1 H), 7.27–7.40 (m, 3 H), 7.58–7.59 (m, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 12.8, 32.6, 64.0, 98.3, 118.9, 121.3, 125.2, 125.3, 126.8, 126.9, 129.3, 137.4, 143.4, 146.4, 147.0, 158.1. HRMS (ESI) m/z calc'd for $C_{18}H_{15}N_4OS$ [M+H]+: 335.0961, found 335.0962. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 5.79 (minor) and 6.48 min (major).

(*R*)-6-Amino-1,4-dihydro-1,4-diphenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (**7q**): White solid, m.p. 171–172 °C, 91% yield, $[\alpha]_D^{25}$ +15.6 (c 0.5, $CHCl_3$), 86% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 0.75 (t, *J* = 7.2 Hz, 3 H), 1.23–1.30 (m, 1 H), 1.36–1.44 (m, 1 H), 2.04–2.11 (m, 1 H), 2.17–2.24 (m, 1 H), 4.64 (br. s, 3 H), 7.21–7.24 (m, 3 H), 7.28–7.33 (m, 3 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 7.63 (d, *J* = 7.6 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 158.1, 150.3, 143.7, 142.3, 137.6, 129.2, 128.8, 127.9, 127.6, 126.7, 121.3, 119.1, 97.9, 63.9, 37.6, 29.5, 21.4, 13.8.. HRMS (ESI) m/z calc'd for $C_{22}H_{21}N_4O$ $[M+H]^+$: 357.1710, found 357.1716. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 5.00 (minor) and 5.58 min (major).

Preparation of compound 10: To a mixture of (*R*)-6-amino-4-(4-chlorophenyl)-1,4-dihydro-3-methyl-1-phenyl-pyrano[2,3-c]pyrazole-5-carbonitrile **7c** (726 mg, 2.0 mmol) and $AlCl_3$ (533 mg, 4.0 mmol) in methylene chloride (20 mL) was added cyclohexanone (393 mg, 4.0 mmol). Then the reaction solution was heated to reflux until the disappearance of starting material **7c** (monitored by TLC). After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc as the eluent) to furnish the corresponding product **10** (753 mg).

(*R*)-5-Amino-4-(4-chlorophenyl)-1-phenyl-3-methyl-1,4,6,7,8,9-hexahydropyrazolo[4',3':5,6]pyrano[2,3-b]quinoline (**10**): White solid, m.p. 288–290 °C, 85% yield, $[\alpha]_D^{20}$ 109.5 (c 0.5, $CHCl_3$), 99% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.72 (br. s, 4 H), 1.94 (s, 3 H), 2.10–2.24 (m, 2 H), 2.68 (br. s, 2 H), 4.05 (br. s, 2 H), 4.86 (s, 1 H), 7.13–7.21 (m, 5 H), 7.33 (t, *J* = 8.0 Hz, 2 H), 7.76 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 13.1, 22.1, 22.4, 22.8, 32.3, 37.0, 98.3, 98.4, 113.8, 120.8, 125.9, 129.0, 129.1, 129.2, 133.0, 138.0, 141.8, 145.6, 145.7, 152.0, 154.4, 154.8. HRMS (ESI) m/z calc'd for $C_{26}H_{24}ClN_4O$ $[M+H]^+$: 443.1633, found 443.1639. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 6.78 (major) and 8.97 min (minor).

Conclusions

In conclusion, we have developed a facile organocatalytic enantioselective synthesis of chiral dihydropyrano[2,3-c]pyrazoles through the cascade Michael addition/cyclization reaction of 4-benzylidenepyrazol-5(4*H*)-ones and malononitrile. Under the catalysis of a (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine-based bifunctional squaramide, the cascade reaction of a broad range of 4-benzylidenepyrazol-5(4*H*)-ones and malononitrile took place smoothly to furnish dihydropyrano[2,3-c]pyrazoles in satisfactory yields with 71–99% ee.

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Notes and references

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