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ARTICLE

Enantioselective Synthesis of Pyrano[2,3-*c*]pyrrole via Organocatalytic [4+2] Cyclization Reaction of Dioxopyrrolidines and Azlactones

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An enantioselective [4+2] cyclization reaction of dioxopyrrolidines and azlactones has been successfully developed through a squaramide catalysis strategy. This protocol provides an efficient and mild access to obtain pyrano[2,3-c]pyrrole scaffold containing contiguous quaternary and tertiary stereogenic centers in excellent yields (up to 99%) with high levels of diastereo- and enantioselectivity (up to 99% ee). Two possible pathways were proposed to explain the observed stereoselectivity.

Introduction

Azlactones are becoming to a class of important reactants in organic synthesis because of their multiple reactive sites,[1] endowing with both nucleophilic and electrophilic properties due to their interconvertible keto and enol forms, which have been widely investigated for the enantioselective synthesis of amino acids containing a quaternary stereocenter.[2] Briefly, Oxazole-5-(4*H*)-ones represent a class of synthetically robust and versatile building blocks enabling either [2+n] by utilizing C4, C5 reactivity,[3,5,6] [3+n] cycloadditions by activating as 1,3-dipoles and other additive reactions.[4] Among these reactions, the catalytic asymmetric [2+4] cyclizations of azlactones using its C4, C5-reactivity have provided an efficient strategy to access cyclic carbonyl compound containing amino acid units. Encouraged by the pioneering study of Gong,[5a] Feng[5b] and Terada,[5c] lots of pyrane[5] or dihydrocoemarins[6] and their derivatives were constructed through catalytic asymmetric [2+4] cyclizations of azlactones (Scheme 1a).

Despite these elegant works of azlactones, considerable attention devoted to assemble pharmaceutically relevant framework is still highly desirable. Pyrrole can be found as a substructure in many natural and synthetic products, many of which exhibit interesting biological activities.[7] Fusion of dihydropyranone with a privileged pharmacophore pyrrolidone provides new synthetic possibilities for drug development. Furthermore, such bicyclic backbones are also found in natural and synthetic products, displaying marvellous bioactivities (Fig. 1).[8] Nevertheless, the strategy to synthesis pyrano-pyrrole via [4+2] cycloaddition of azlactone has been not reported in the literature. Herein, we disclose a mild and concise way to synthesis enantiomerically enriched pyrano[2,3-*c*]pyrrole derivatives via catalytic asymmetric [4+2] cyclizations of azlactones (Scheme 1b).

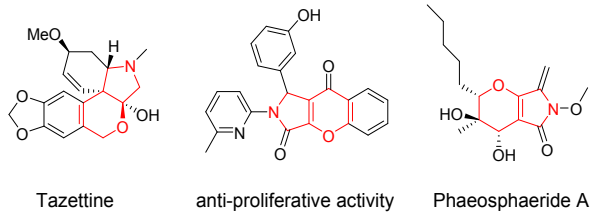
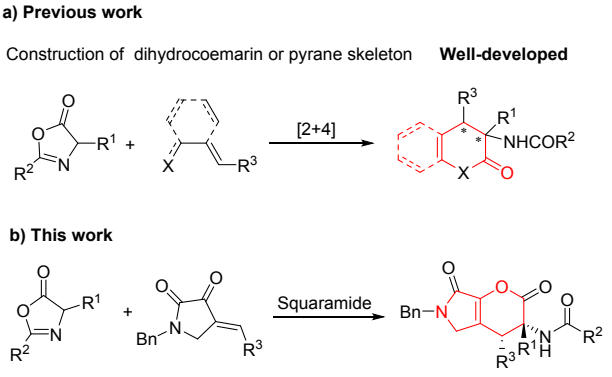


Figure 1 Natural and synthetic products containing the pyrane-pyrrole moiety.



Scheme 1 Synthesis of pyrane derivatives via [4+2] cyclizations of azlactones.

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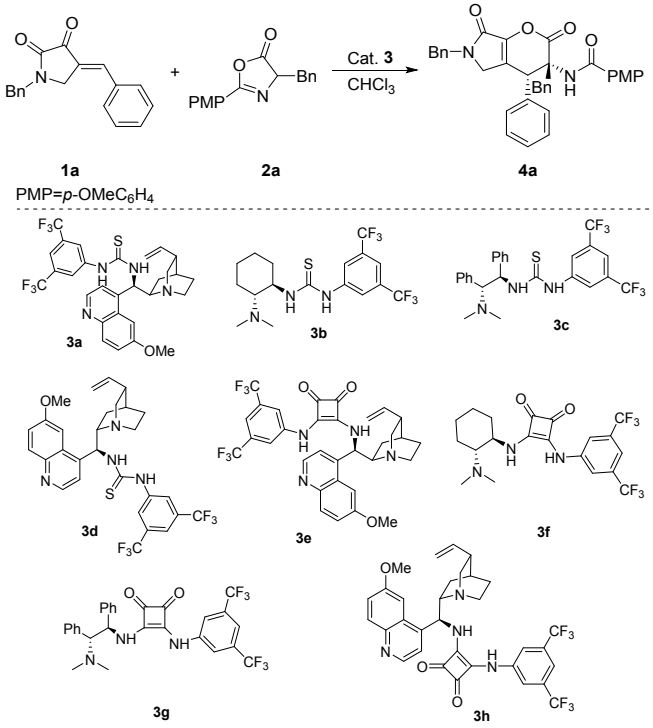
Results and discussion

Base on the above considerations, our initial investigations were carried out using a series of tertiary amine-thioureas catalysts (**3a**-**3d**) for the model reaction of 1-benzyl-4-benzylidenepyrrolidine-2,3-dione **1a** and azlactone **2a** in $CHCl_3$ at room temperature. Generally, those catalysts effectively promoted the model reaction to obtain the corresponding product **4a** as single diastereoisomer with moderate yield after 6 hours, but with low enantioselectivity (Table 1, entries 1-4). Pleasingly, when squaramide scaffolds was introduced in these catalysts for strengthening the hydrogen-bonding effect, they led to an increase in the enantioselectivity of the process and have a little effect on the yield of the reaction (entries 5-8). It was found that catalyst **3e** was the most potent in $CHCl_3$ at room temperature, and the cycloaddition product **4a** was formed in 75% yield with >20:1 dr and 83% *ee* (entry 5).

Table 1 Evaluation of catalysts[a]

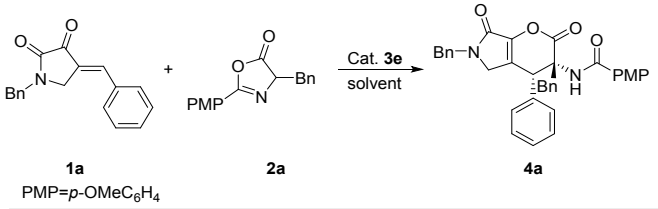


Entry	Cat.	Solvent	Yield[b] (%)	dr[c]	ee[d] (%)
1	**3a**	$CHCl_3$	84	>20:1	46
2	**3b**	$CHCl_3$	63	>20:1	34
3	**3c**	$CHCl_3$	66	>20:1	40
4	**3d**	$CHCl_3$	88	>20:1	-26
5	**3e**	$CHCl_3$	75	>20:1	83
6	**3f**	$CHCl_3$	50	>20:1	70
7	**3g**	$CHCl_3$	70	>20:1	75
8	**3h**	$CHCl_3$	72	>20:1	-70

[a] The reaction was conducted with 0.05 mmol of **1a**, 0.06 mmol of **2a** and 0.005 mmol of **3** in 1.0 mL $CHCl_3$. [b] Isolated yields after column chromatography on silica gel. [c] Only a single diastereoisomer was observed by crude ^{1}H NMR. [d] Determined by chiral HPLC analysis on a chiral column

Since the squaramide catalyst **3e** provided the best initial yield and enantioselectivity for the synthesis of **4a** from **1a** and **2a**, further optimization was pursued with this scaffold. Among the different kinds of solvents (Table 2, entries 1-6), $CHCl_3$ was proved to be the most effective in increasing both the yield and enantioselectivity of **4a** (entry 1). Lowering the reaction temperature allowed further improvement in the selectivity of reaction (entries 7-9), when the reaction was performed at -20 °C, **4a** was formed with 92% *ee*, albeit at a slight decrease of the reaction yield. Subsequently, the optimization efforts were directed towards the reaction concentration and time (entry 10). To our delight, both yield and *ee* have been improved by prolonged time and reduced concentration of reactant. Furthermore, expanding the amount of reaction could increase in yield to 91% was observed while maintaining the enantioselectivity (entry 11).

Table 2 Optimization of the reaction conditions[a]



Entry	Solvent	Temp (°C)	time	Yield[b] (%)	ee[c] (%)
1	$CHCl_3$	rt	6h	75	83
2	CH_2Cl_2	rt	0.5h	59	74
3	DCE	rt	2h	55	67
4	CCl_4	rt	48h	20	59
5	Toluene	rt	5.5h	70	73
6	THF	rt	1h	61	38
7	$CHCl_3$	0	6h	80	89
8	$CHCl_3$	-10	6h	87	90
9	$CHCl_3$	-20	6h	83	92
10[d]	$CHCl_3$	-20	48h	85	94
11[e]	$CHCl_3$	-20	48h	91	94

[a] The reaction was conducted with 0.05 mmol of **1a**, 0.06 mmol of **2a** and 0.005 mmol of **3e** in 1.0 mL solvent. [b] Isolated yields after column chromatography on silica gel. [c] Determined by chiral HPLC analysis on a chiral column. Only a single diastereoisomer was observed by crude ^{1}H NMR. [d] In 2.0 mL $CHCl_3$. [e] The reaction was conducted with 0.10 mmol of **1a**, 0.12 mmol of **2a** and 0.01 mmol of **3e** in 4.0 mL$CHCl_3$.

Having established the optimum reaction conditions, we next investigated the scope of dioxopyrrolidines **1** which were employed to react with azlactone **2a**. As shown in Table 3, gratifyingly, excellent yields and enantioselectivities (all cases >20:1dr) were obtained with substrates containing various aryl and heteroaryl groups (**4a**-**4w**) at the terminal

position of the dioxopyrrolidines. With *para*-substitution bearing either electron-donating or electron-withdrawing groups, these substrates proceeded smoothly to desired products **4b**-**4h** in good yields as well as enantioselectivities. As for the substrates with *meta*-position, the corresponding products **4i-4m** were afforded in good to excellent yields (82%-99%), with excellent enantioselectivities (92-95% *ee*). For *ortho*-substituent bearing electron-withdrawing, **4n** and **4o** were delivered in good yields (83% and 70% respectively) and enantioselectivities (95% and 90% *ee* respectively), especially, product **4p** with electron-donating substituent was delivered in excellent yield and best enantioselectivity (90% yield and 99% *ee*). Moreover, double substituents (3,5-Cl_2, 2,4-Cl_2, 2-Me-4-F) could be introduced into aromatic ring of Ar group with a slight effect on the yield and stereoselectivity, and no significant electronic effect on the aromatic moiety was observed, except that a slightly lower ee value (73%) was obtained for the 2,4-Me_2 substituent substrate **4s**. The reaction of sterically more congested dioxopyrrolidines **1u** and **1v** also acquired relevant products **4u** and **4v** in 80% yield with 85% *ee* and 61% yield with 99% *ee* respectively. In addition, the scope of dioxopyrrplidine could be extend to hetero substrate 1-benzyl-4-(thiophen-2-ylmethylene)pyrrolidine-2,3-dione **1w**, furnished the cycloaddition product **4w**. The absolute configuration of product 4d was determined as 3*R*,4*R* by X-ray crystallography[9] (Fig. 2), and the other products were assigned by analogy.

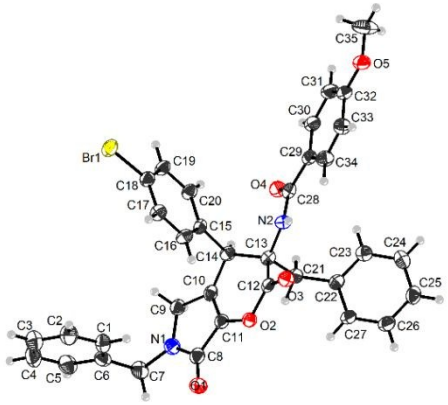
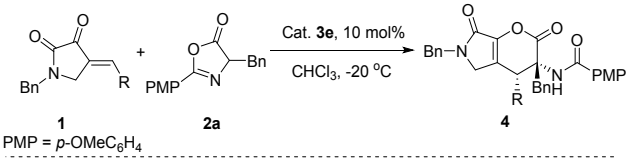


Figure 2 X-ray crystal structure of **4d**

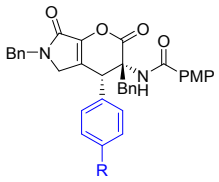
Encouraged by the above mentioned results, the substrate scope of azlactones **2** was investigated. Satisfyingly, substituent R^1 was examined to afford the corresponding adducts, both benzyl and alkyl groups were well tolerated. Azlactones with substituent on the phenyl ring in the R^1 group could be smoothly converted to corresponding products **5a**-**5c** in moderate yields and *ee* (70-83% yields and 77-92% *ee*). For alkyl substituted **5d** and **5e**, excellent *ee* values (93% *ee*, 90% *ee*) and moderate yields (71% and 63%) were obtained. Furthermore, azlactones with various substitutions on the phenyl ring in the R^2 group were also evaluated and exhibited good tolerance for the reaction, but product **5g** obtained sharply decreased *ee* value and yield. In addition, azlactone **2h** with a benzyl group and a benzene group was well tolerated in the reaction, giving 84%

Table 3 Substrate scope of dioxopyrrolidines **1**[a]

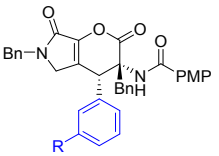


1 2a 4

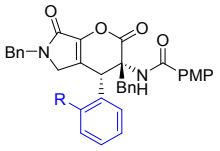
PMP = *p*-$OMeC_6H_4$



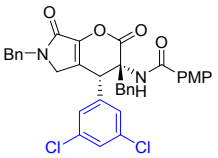
4a R = H, 91% yield, 94% *ee*, 48h
4b R = F, 99% yield, 91% *ee*, 48h
4c R = Cl, 74% yield, 95% *ee*, 24h
4d R = Br, 74% yield, 95% *ee*, 24h
4e R = CF_3, 89% yield, 95% *ee*, 72h
4f R = NO_2, 73% yield, 98% *ee*, 24h
4g R = CH_3, 89% yield, 95% *ee*, 24h
4h R = OMe, 73% yield, 90% *ee*, 48h



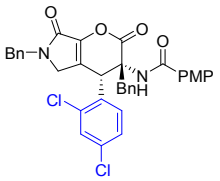
4i R = F, 99% yield, 94% *ee*, 48h
4j R = Cl, 99% yield, 95% *ee*, 48h
4k R = Br, 82% yield, 95% *ee*, 72h
4l R = CH_3, 99% yield, 95% *ee*, 48h
4m R = OMe, 87% yield, 92% *ee*, 72h



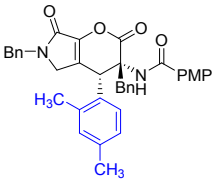
4n R = Cl, 78% yield, 95% *ee*, 24h
4o R = Br, 71% yield, 90% *ee*, 48h
4p R = CH_3, 90% yield, 99% *ee*, 48h



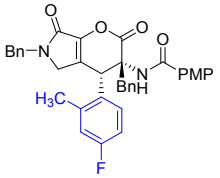
4q 68% yield, 93% *ee*, 48h



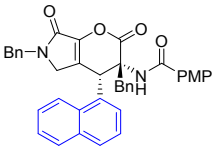
4r 79% yield, 99% *ee*, 48h



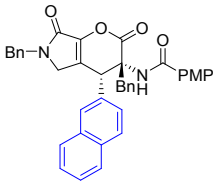
4s 68% yield, 73% *ee*, 36h



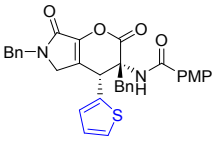
4t 81% yield, 98% *ee*, 48h



4u 76% yield, 85% *ee*, 72h



4v 61% yield, 99% *ee*, 48h

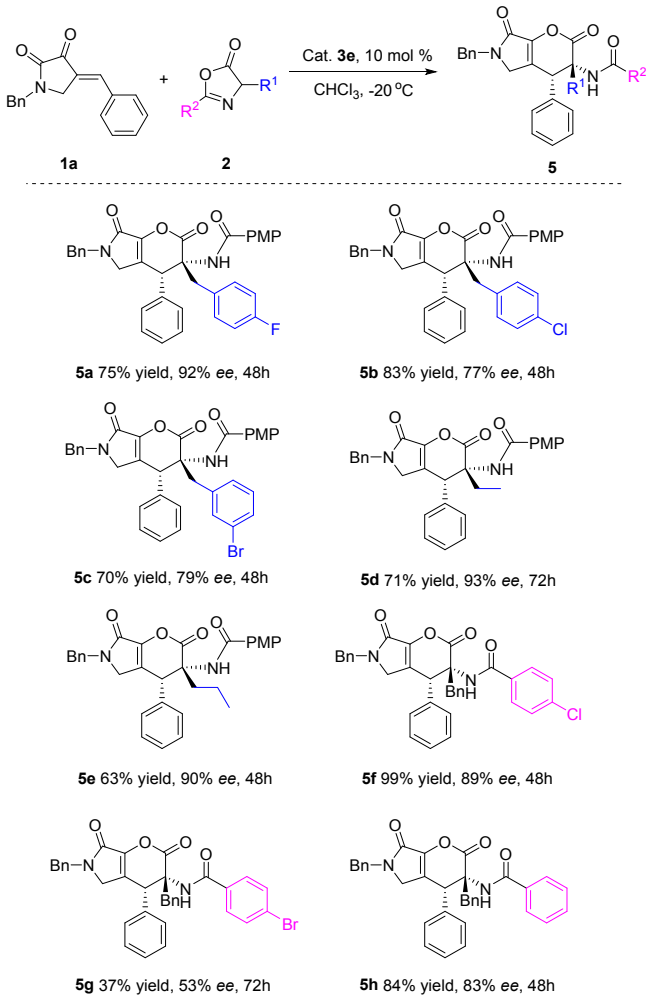


4w 75% yield, 71% *ee*, 72h

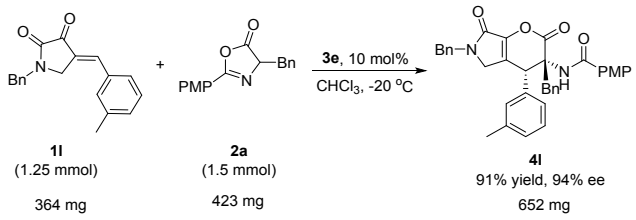
[a] The reaction was conducted with 0.10 mmol of **1**, 0.12 mmol of **2a** and 0.01 mmol of **3e** in 4.0 mL $CHCl_3$. Products **4** were obtained in isolated yields. *ee* was determined by chiral HPLC analysis on a chiral column. Only a single diastereoisomer was observed by crude ^1H NMR.

yield and 83% *ee*. In all cases, only a single diastereoisomer was observed.

Table 4 Substrate scope of azlactones **2**[a]

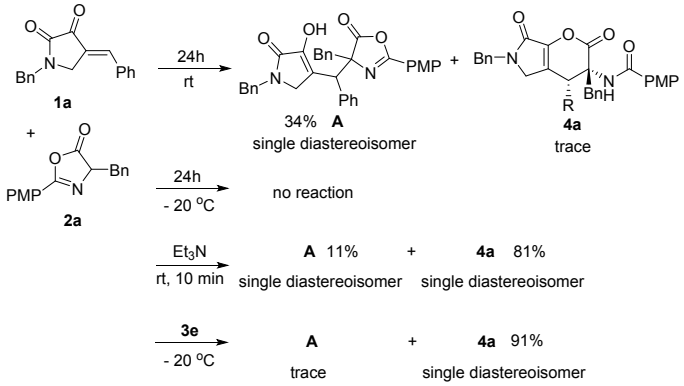


[a] The reaction was conducted with 0.10 mmol of **1a**, 0.12 mmol of **2** and 0.01 mmol of **3e** in 4.0 mL $CHCl_3$. Products **5** were obtained in isolated yields. *ee* was determined by chiral HPLC analysis on a chiral column. Only a single diastereoisomer was observed by crude ^1H NMR.

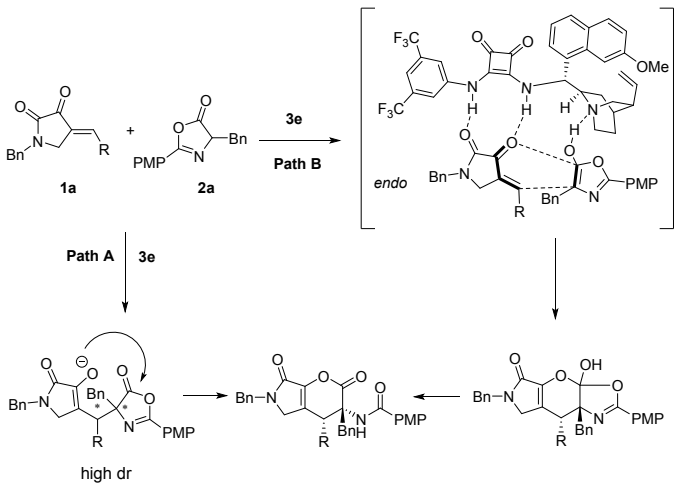


Scheme 2 A larger-scale synthesis of **4l**

To show the synthetic potential of catalytic protocol, a large-scale reaction of this transformation was performed by using 1.25 mmol of **1l** and the corresponding adduct **4l** was obtained in excellent yield (91%) and (94% *ee*) stereoselectivity (Scheme 2).



Scheme 3 Control experiments



Scheme 4 Plausible reaction pathways

In order to investigate the reaction pathway, the control experiment was carried out (Scheme 3). Actually, there have a background reaction in this transformation, Michael adduct **A** with complete diastereoselectivity can be isolated under catalyst-free at room temperature. No reaction occurred when the temperature dropped to -20 °C. The reaction can be promoted by an organic base such as Et_3N, afforded product **4a** and Michael adduct **A**, both of them were as a single diastereoisomer, this catalytic process is similar to Terada's observation [5c], It can be considered that the diastereoselectivity is an intrinsic feature of the reaction. Under the catalysis of the bifunctional catalyst, Michael adduct intermediates were trace (from TLC) in most cases. Furthermore, considering Feng's plausible transition state[5b], we could not exclude the possibility that this reaction may conduct via an inverse-electron-demand hetero-Diels–Alder reaction process. Therefore, two plausible reaction pathways are proposed to explain the reaction process as shown in

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Scheme 4. In path A, a catalysed Michael addition as the stereo-determining step, followed by intramolecular O-acylation of the new born enolate and opening of the oxazolone ring. In path B, under the catalysis of the bifunctional catalyst, the inverse-electron-demand hetero-Diels-Alder (IEDDA) reaction may proceed in an *endo* way affording intermediate, followed by ring opening to furnish the target product.

Conclusions

In conclusion, we have developed a highly stereoselective [4+2] cyclization reaction of dioxopyrrolidines and azlactones by a squaramide activation strategy. A wide range of dioxopyrrolidines and azlactones were well tolerated to give the corresponding multiply substituted pyrano[2,3-*c*]pyrrole containing adjacent tertiary and quaternary stereogenic centers in high yields (up to 99%) with excellent diastereo- and enantioselectivity (up to 99% *ee*, all cases >20:1 dr). Two possible pathways were proposed to explain the observed stereoselectivity. Further studies on the synthetic application and biological activity of cyclization products are currently ongoing and will be reported in due course.

Experimental

General Procedure for Asymmetric [4+2] Cyclization Reaction

Dioxopyrrolidines **1** (0.1 mmol, 1.0 equiv.) and **3e** (0.01 mmol, 0.1 equiv.) in $CHCl_3$ (3.0 mL) were cooled to -20 °C, then added azlactones **2** (0.12 mmol, 1.2 equiv.) in $CHCl_3$ (1.0 mL). The reaction stirred at -20 °C for the time indicated at Table 3 or Table 4, and then the solvent was removed under vacuum to give a residue, which was purified by silica gel chromatography to yield the desired product **4** or **5**. The enantiomeric ratio was determined by HPLC analysis on chiral column.

N-((3*R*,4*R*)-3,6-dibenzyl-2,7-dioxo-4-phenyl-2,3,4,5,6,7-hexahydropyrano[2,3-c]pyrrol-3-yl)-4-methoxybenzamide (4a). White solid, 50.7 mg, 91% yield, [α]20 D–43.3 (*c* 0.492, CH_2Cl_2), 94% *ee*. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.28 (m, 6H), 7.21 (d, *J* = 5.9 Hz, 6H), 7.14 (d, 4H), 6.79 (d, *J* = 8.3 Hz, 2H), 6.59 (s, 1H), 5.05 (s, 1H), 4.77 (d, *J* = 14.8 Hz, 1H), 4.61 (d, *J* = 14.8 Hz, 1H), 4.25 (d, *J* = 13.6 Hz, 1H), 3.94 (d, *J* = 18.8 Hz, 1H), 3.78 (s, 3H), 3.70 (d, *J* = 18.8 Hz, 1H), 3.34 (d, *J* = 13.6 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 167.7, 167.3, 162.3, 162.1, 141.5, 136.2, 135.7, 134.0, 130.1, 129.1, 129.0, 128.5, 128.5, 128.4, 128.3, 128.1, 127.8, 127.7, 126.9, 113.8, 66.2, 55.4, 48.0, 47.7, 46.9, 39.7. HRMS (ESI) *m/z* calculated for $C_{35}H_{30}N_2O_5$ [M+H] $^+$: 559.2227, found 559.2222. HPLC analysis: (IB column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 15.65 (minor), 20.58 (major).

N-((3*R*,4*R*)-6-benzyl-3-(4-fluorobenzyl)-2,7-dioxo-4-phenyl-2,3,4,5,6,7-hexahydropyrano[2,3-c]pyrrol-3-yl)-4-methoxybenzamide (5a). White solid, 43.2 mg, 75% yield, [α]20 D-32.7 (*c* 0.412, CH_2Cl_2), 92% *ee*. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 – 7.16 (m, 6H), 7.11 (d, *J* = 5.5 Hz, 3H), 7.00 (dt, *J* = 8.4, 4.5 Hz, 4H), 6.80 (t, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.7 Hz, 2H), 6.45 (s, 1H), 4.91 (s, 1H), 4.68 (d, *J* = 14.9 Hz, 1H), 4.50 (d, *J* = 14.9 Hz, 1H), 4.13 (d, *J* = 13.9 Hz, 1H), 3.83 (d, *J* = 18.9 Hz, 1H), 3.69 (s, 3H), 3.60 (d, *J* = 18.8 Hz, 1H), 3.19 (d, *J* = 13.8 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 167.6, 167.3, 163.5, 162.4, 162.0, 161.1, 141.5, 136.1, 135.5, 131.7, 129.8, 129.7, 129.1, 129.0, 128.5, 128.4, 128.3, 128.3, 128.1, 127.7, 126.7, 115.5, 115.3, 113.8, 66.1, 55.4, 47.9, 47.6, 46.9, 38.8.HRMS (ESI) *m/z* calculated for $C_{35}H_{29}FN_2O_5$ [M+H]$^+$:577.2133, found:577.2122. HPLC analysis: (IB column, Hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 22.47 (minor), 25.06 (major).

Conflicts of interest

There are no conflicts to declare.

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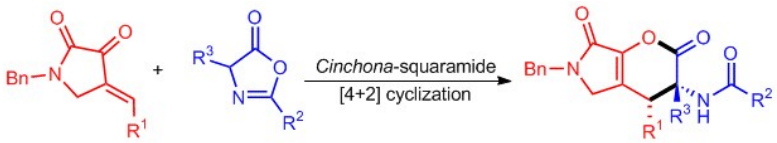
The present work provides a simple and efficient access to chiral Pyrano[2,3-c]pyrrole via asymmetric [4 + 2] cyclization reaction catalyzed by a cinchona-squaramide catalyst.



R^1 = aryl R^2 = aryl
R^3 = alkyl, aryl

up to 99% yield, up to 99% ee, all cases >20/1 dr
31 examples