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Original article

Enantioselective synthesis of functionalized fluorinated dihydropyrano [2,3-c]pyrazoles catalyzed by a simple bifunctional diaminocyclohexane-thiourea

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ABSTRACT

Enantioselective synthesis of functionalized fluorinated dihydropyrano[2,3-c]pyrazoles has been achieved *via* a diaminocyclohexane-thiourea catalyzed cascade Michael addition and Thorpe-Ziegler type cyclization in high yields (up to 98%) with moderate to good enantioselectivity (up to 90% *ee*).
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1. Introduction

The incorporation of fluorine atom(s) or fluorine-containing moieties into organic molecules would affect their lipophilicity and spatial structure, thus emanating unique physical, chemical and biological properties, which can lead to potential applications in materials, medicinal, pharmaceutical and agrochemical sciences [1]. In particular, the replacement of metabolically active hydrogen atoms with fluorine atoms (or CF_3) is commonly used in contemporary medicinal chemistry to improve metabolic stability, bioavailability and protein–drug interactions [2]. This strategy has been illuminated in the organocatalytic asymmetric synthesis of fluorinated molecules and several important methods have been developed in the last decade [3].

Pyrano[2,3-c]pyrazoles are a large class of heterocyclic compounds possessing many important biological activities, such as analgesic, anti-inflammatory, anti-tumor, insecticidal activities and so on [4]. Since the first reaction for the synthesis of pyrano[2,3-c]pyrazole derivatives from 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene was reported by Junek in 1973 [5a], a large number of efficient synthetic methods to construct dihydropyrano[2,3-c]pyrazole derivatives have been developed [5]. Very recently, Zhao has reported the first organocatalyzed enantioselective method for the synthesis of these compounds using the cinchona alkaloid as the catalyst [6]. However, to the best of our knowledge, no chiral fluorinated dihydropyrano[2,3-c]pyrazoles have been reported up to date [7]. Herein, based on some previous studies in our group [8], we would like to present an efficient catalyst system for the cascade Michael addition–cyclization using diaminocyclohexane-thioureas [9] as a bifunctional catalyst providing a series of novel chiral fluorinated dihydropyrano[2,3-c]pyrazoles.

2. Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, with TMS as an internal standard. ^{19}F NMR spectra were recorded at 282 MHz with $CFCl_3$ as an external standard. IR spectra were recorded in cm^{-1}. Melting points were determined on an apparatus, which was not corrected. All solvents were distilled prior to use unless otherwise noted. All reactions sensitive to moisture or oxygen were conducted under an atmosphere of nitrogen or argon.

To a mixture of **1** (0.1 mmol, 1.0 equiv.) and catalyst **3c** (0.01 mmol, 0.1 equiv.) in $CHCl_3$ (2 mL) was added **2** (0.12 mmol, 1.2 equiv.). Then the reaction solution was vigorously stirred at 0 °C and monitored by TLC analysis. After the reaction was complete, the mixture was concentrated and purified by flash column chromatography on silica gel (petroleum ether/EtOAc as

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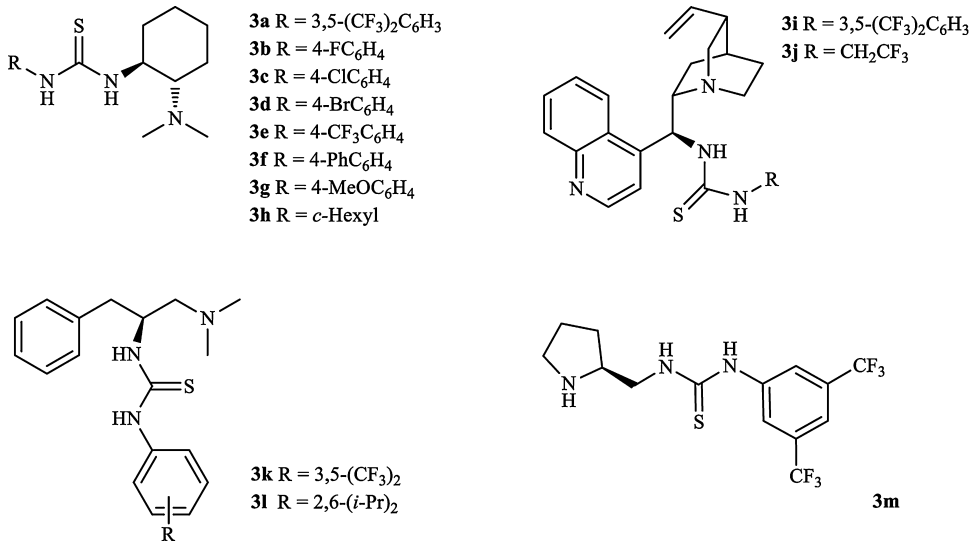


Fig. 1. Thiourea catalysts evaluated in this study.

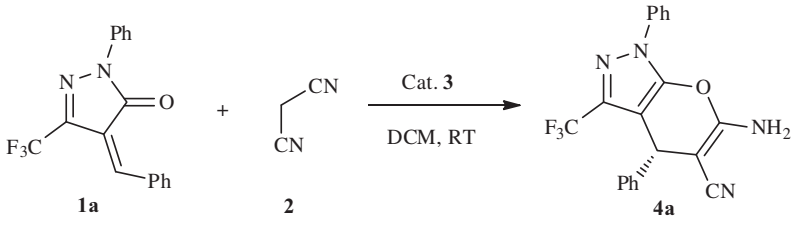
the eluent) to furnish the corresponding product **4**. The data of compounds **4a**–**p** can be found in Supporting information.

3. Results and discussion

Initially, the Takemoto's catalyst **3a** (Fig. 1) was investigated in the model reaction between (*Z*)-4-benzylidene-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5(4*H*)-one (**1a**) and malononitrile (**2**) in dichloromethane (DCM) at room temperature. The reaction gave the desired cyclic product **4a** in an excellent yield; however, a poor enantioselectivity (57% *ee*) was also observed (Table 1, entry 1). In order to enhance the enantioselectivity, several other diaminocyclohexane-thiourea catalysts with weaker H-bond donating ability on the thiourea were screened. As expected, the yields that were more correlative with the tertiary amine altered little with these catalysts but higher enantioselectity could be obtained with catalysts **3b**–**f** (entries 2–7). With the *c*-hexyl substituted catalyst **3h**, a lower *ee* value was obtained (entry 8). Encouraged by the above improvement made with the modified diaminocyclohexane-thiourea catalysts, additional catalysts **3h**–**m** derived from amino acids and the cinchona alkaloid were also synthesized and evaluated in this reaction. We found that the cinchona alkaloid-derived bifunctional thiourea catalysts **3i** and **3j** both gave poor enantioselectivity (entries 9 and 10) probably due to their strong base effect and with the amino acid-based catalysts **3k**, **3l** and **3m**; similar inferior results were also obtained. For all of the reactions, the desired products could be obtained in high yields (>90%) in no more than 50 min.

Then the reactions in various solvents were screened. The results were summarized in Table 2. Generally, the reactions

Table 1
Screening of the catalysts.[a]



Entry	Cat.	Time (min)	Yield (%)[b]	*ee* (%)[c]
1	**3a**	40	95	57
2	**3b**	40	94	71
3	**3c**	30	95	72
4	**3d**	30	94	70
5	**3e**	50	93	70
6	**3f**	40	94	64
7	**3g**	20	93	53
8	**3h**	20	90	46
9	**3i**	50	93	14
10	**3j**	40	92	33
11	**3k**	30	90	5
12	**3l**	40	91	8
13	**3m**	40	90	15

[a] All the reactions were carried out with **1a** (0.1 mmol) and **2** (0.12 mmol) in the presence of **3** (0.01 mmol) in CH_2Cl_2 (2.0 mL) at room temperature.
[b] Yields of isolated products.
[c] Determined by chiral HPLC analysis.

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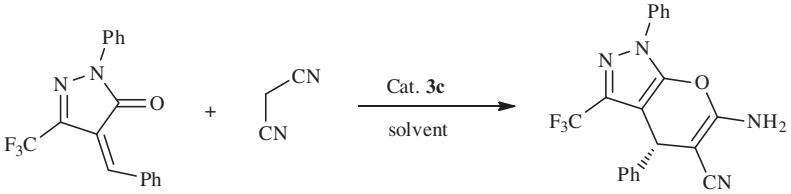
Table 2
Optimization of the reactions in various solvents under different temperatures.[a]



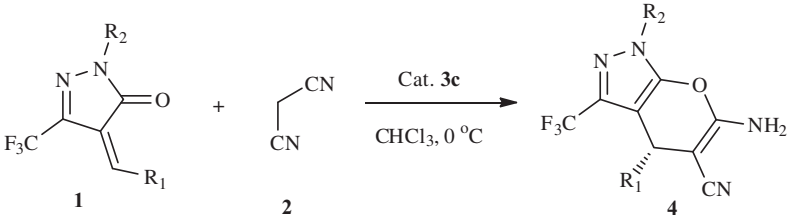
1a **2** **4a**

Entry	Solvent	Time (h)	Yield (%)[b]	*ee* (%)[c]
1	Et_2O	1	90	53
2	Toluene	1.5	92	67
3	$CHCl_3$	1	95	75
4	*n*-Hexane	3	–	–
5	THF	3.5	93	30
6	Xylenes	3.5	60	53
7	PhCl	0.5	92	67
8	$ClCH_2CH_2Cl$	0.5	90	63
9	CCl_4	3.5	57	55
10	$Cl_2CHCHCl_2$	0.5	95	67
11[d]	$CHCl_3$	6	95	81
12[e]	$CHCl_3$	12	94	79
13[f]	$CHCl_3$	24	93	80

[a] Unless otherwise specified, all the reactions were carried out with **1a** (0.1 mmol) and **2** (0.12 mmol) in the presence of **3c** (0.01 mmol) in solvent (2.0 mL) at room temperature.
[b] Yields of isolated products.
[c] Determined by chiral HPLC analysis.
[d] The reaction was carried out at 0 °C.
[e] The reaction was carried out at −5 °C.
[f] The reaction was carried out at −10 °C.

proceeded smoothly in most solvents providing **4a** in excellent yields except in those that the substrates have poor solubility in such as *n*-hexane, xylenes and CCl_4 (entries 4, 6, 9). Further investigation showed that the reaction worked the best in chloroform, which gave the desired product in 95% yield and 75% *ee* (entry 3). Lowering the reaction temperature from room temperature to 0 °C increased the *ee* value to 81% while the excellent yield was maintained (entry 11). However, even lower

Table 3
Investigation of reaction scope.[a]



1 **2** **4**

Entry	R_1, R_2 (**1**)	Time (h)	Product	Yield (%)[b]	*ee* (%)[c]
1	4-OMe-C_6H_4, Ph	10	**4b**	93	90
2	4-Me-C_6H_4, Ph	8	**4c**	92	88
3	4-F-C_6H_4, Ph	6.5	**4d**	92	80
4	4-Cl-C_6H_4, Ph	6.5	**4e**	92	79
5	4-Br-C_6H_4, Ph	12	**4f**	89	71
6	4-NO_2-C_6H_4, Ph	8	**4g**	86	47
7	3-Br-C_6H_4, Ph	8	**4h**	90	75
8	2-Br-C_6H_4, Ph	8	**4i**	98	60
9	2-Furyl, Ph	10	**4j**	88	77
10	Ph, 4-Me-C_6H_4	8	**4k**	90	78
11	Ph, 4-OMe-C_6H_4	8	**4l**	82	76
12	Ph, 4-Br-C_6H_4	12	**4m**	90	65
13	Ph, 4-Cl-C_6H_4	8	**4n**	93	63
14	Ph, 3-Cl-C_6H_4	7.5	**4o**	93	67
15	Ph, 2-Cl-C_6H_4	8.5	**4p**	92	35

[a] Unless otherwise specified, all the reactions were carried out with **1** (0.1 mmol) and **2** (0.12 mmol) in the presence of **3c** (0.01 mmol) in $CHCl_3$ (2.0 mL) at 0 °C.
[b] Yields of isolated products.
[c] Determined by chiral HPLC analysis.

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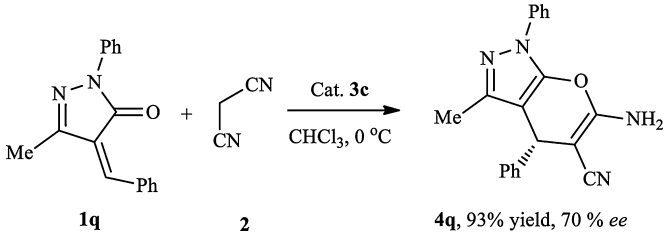


1q 2 4q, 93% yield, 70 % *ee*

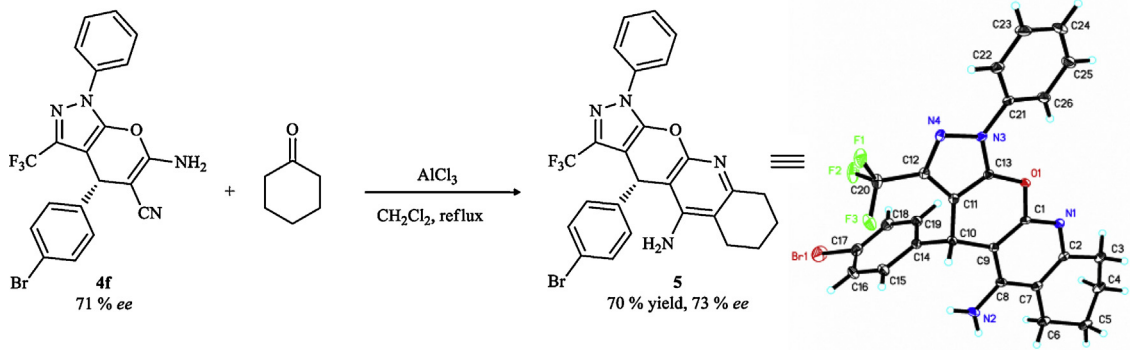
Scheme 1. Reaction of the non-fluorinated substrate **1q**.

temperatures brought no improvement in enantioselectivity but led to a prolonged reaction time (entry 13). As a consequence, the optimal condition for this Michael addition–cyclization was obtained with 10 mol % of **3c** in $CHCl_3$ at 0 °C.

Having established the optimal conditions for the cascade Michael addition–cyclization, we next explored the scope of the reaction and the representative results are listed in Table 3. For pyrazoles with different R_1 substituents, excellent yields and good *ee* values could be generally obtained regardless of the electronic nature or positions of the substituents on the phenyl group of R_1 except the substrates with a strong electron-withdrawing nitro group or *ortho*-substituents (entries 1–8). This reaction was also tolerant with a heteroaromatic ring by giving the product **4g** in good yield and enantioselectivity (entry 9). A similar substituent effect was observed while changing the substituents on R_2. Although slightly lower *ee* values were obtained with this type of substrates, good enantioselectivity could also be obtained with electro-donating substituents (entries 10–15).

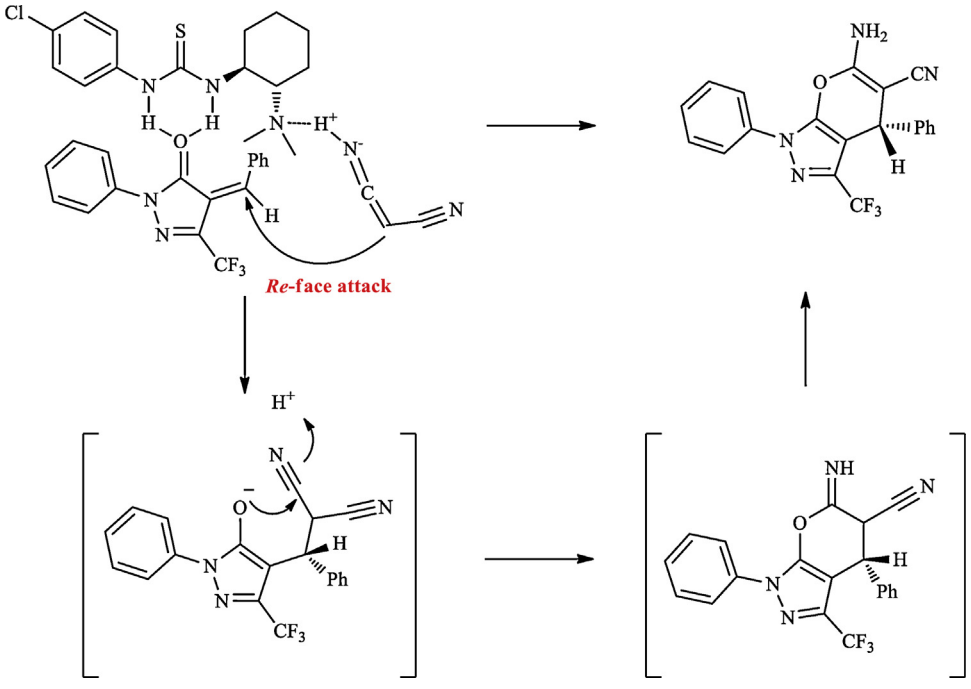
Notably, although in a prolonged reaction time, the non-fluorinated substrate **1q** also proceeded efficiently to give the desired product **4q** in excellent yields with slightly lower *ee* values (Scheme 1), which provides an easy access to this kind of important intermediates.

In an effort to realize the goal of generating biologically interesting products, further transformations of the chiral pyrano[2,3-c]pyrazole products **4** obtained above were then investigated (Scheme 2). With aluminum chloride as a catalyst [10], the Friedländer reaction of the pyrano[2,3-c]pyrazole **4f** with cyclohexanone afforded the heterocyclic product **5** in 70% yield without sacrificing the stereo-integrity. The absolute configuration of **5** was then confirmed by X-ray crystallography to be *S* [11] and the absolute configuration of product **4** was determined in the same manner (Scheme 2). It should be noted that these types of heterocyclic compounds with pyranopyridine scaffold are known to possess potential biological activities, such as antiallergic, anti-



4f 71 % *ee* 5 70 % yield, 73 % *ee*

Scheme 2. Transformation of the product **4f**.



Scheme 3. Proposed catalytic mechanism of the asymmetric Michael addition–cyclization reaction.

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inflammatory, and estrogenic properties [12]. In addition, the compounds containing benzopyrano[2,3-b]pyridine structure also exhibit anti-proliferative, cancer chemopreventive and anti-bacterial (including anti-tubercular) activities [13].

In light of the previous studies and the configuration obtained, a plausible reaction pathway was proposed in Scheme 3 [7]. The bifunctional thiourea catalyst is not only as a base to deprotonate the malononitrile by the tertiary amine moiety but also activates the carbonyl group of 4-aryliden-5-pyrazolones by forming two hydrogen bonds using the N–Hs. When R_1 or R_2 contained electron-donating groups, more powerful hydrogen bonds were formed and herein high *ee* values were achieved. The mechanism could also explain why low *ee* values were obtained with *ortho* substituent on R_2; the big steric hindrance made the hydrogen bonds weaker.

4. Conclusion

In summary, we have developed an asymmetric organocatalytic cascade Michael addition–cyclization reaction using bifunctional diaminocyclohexane-thiourea catalysts. The reactions gave the attractive products in excellent yields and good enantioselectivity under mild reaction conditions, making it a novel and valuable method for the construction of potential biologically active functionalized fluorinated dihydropyano[2,3-c]pyrazoles, which are also important intermediates in medicinal chemistry and can be valuable for the pharmaceutical industry.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2014.01.034.

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[11] X-ray crystal: Triclinic, space group: P-1, Final R indices [I>2sigma(I)]: R_1 = 0.0537, wR_2 = 0.1763; unit cell dimensions: a = 7.6593(12) Å, b = 13.191(2) Å, c = 13.678 (2) Å, α = 67.787(2)°, β = 82.977(3)°, γ = 86.498(2)°; volume: 1269.7(3) Å^3; crystal size: 0.39 mm × 0.30 mm × 0.28 mm; T = 173(2) K; Z, calculated density: 2, 1.416 mg/m^3; reflections collected/unique: 9139/5448 [R(int) = 0.0219]; date/restraints/parameters: 5448/0/316. X-ray analysis of single crystal of 5 was deposited at Cambridge crystallographic data center with CCDC 862430.

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