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Asymmetric fluorination of 4-substituted pyrazolones catalyzed by quinine

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ABSTRACT

An asymmetric fluorination process of 4-substituted pyrazolones catalyzed by quinine is revealed. The reaction afforded a wide range of 4-fluorinated pyrazol-5-ones with excellent yields (up to 98%) and moderate to good enantioselectivities (up to 81% *ee*).

1. Introduction

Pyrazolones, privileged nitrogen containing heterocyclic compounds, are an appealing class of pharmacophores due to their important pharmacological activities, serving as, for example, neuroprotective agents, HIV-1 integrase inhibitors and antipyretic agents (Fig. 1).[1] In order to diversify the pyrazolone-based structures for potential medicinal research, in recent years, much effort has been devoted to the construction of new, potentially bioactive, enantioenriched pyrazolone derivatives, especially 4,4-disubstituted pyrazolone compounds.[2]

Among the strategies developed, the nucleophilic attack of 4-substituted pyrazolones to various appropriate electrophiles represents a more straightforward method to afford 4,4-disubstituted pyrazolones bearing a tetrasubstituted carbon stereocenter. In this respect, Yuan et al. reported the first asymmetric strategy to construct 4,4-disubstituted pyrazolones with the addition of 4-substituted pyrazolones to nitroalkenes catalyzed by a bifunctional aminothiourea.[3] Subsequently, the additions of 4-substituted pyrazolones to the 4-oxo-4-arylbutenoates,[4] alkynones[5] and azodicarboxylates[6] catalyzed by chiral *N*,*N*′-dioxide-metal complexes or to *N*-aryl maleimides[7] and azodicarboxylates[8] by organocatalysis were achieved with high enantioselectivity. In addition, the asymmetric allylic alkylation of 4-substituted pyrazolones was demonstrated by Gong et al.[9] with the combination of a chiral phosphoramidite-palladium complex and a chiral phosphoric acid with allylic alcohols, and by Wang et al.[10] using Morita–Baylis–Hillman carbonates as the alkylation reagent.

Asymmetric fluorination, due to the privileged role of organofluorine compounds in medicinal chemistry, agrochemical, and materials science, has gained increasing attention over the past decade.[11] Given the pharmaceutical significance of both the pyrazolone scaffold and the fluorine subunit, the union of the two privileged structures in an asymmetric fashion would be of potential interest for medicinal research. In this regard, Ma et al. developed an elegant Michael addition/fluorination cascade reaction with 4-nonsubstituted pyrazolones as the starting material.[12] Very recently, we reported an organocatalytic asymmetric Friedel–Crafts addition/fluorination sequence to construct oxindole-pyrazolone conjugates with high stereoselectivity.[13] Although the enantioenriched 4-fluoropyrazolones were obtained by Ma and our previous work, the stereochemistry of the fluorine-containing carbon center was substrate-controlled by a pre-existing vicinal stereogenic center generated by an asymmetric Michael addition or Friedel–Crafts addition event. Zhao et al. also demonstrated a tandem C–H insertion/fluorination process starting with pyrazole

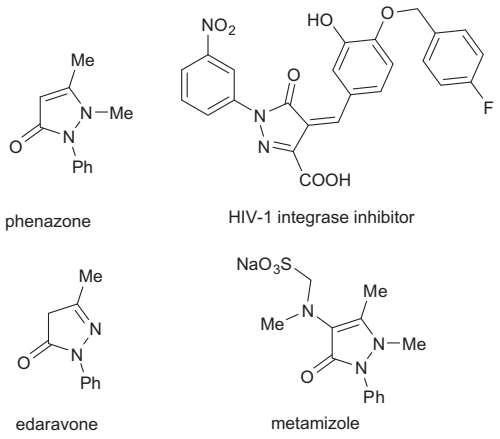

Figure 1. Selected examples of pharmacological active pyrazolone derivatives.

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diazo compounds, but only a specific substrate was fluorinated, promoted by equivalent chiral base.[14] Thus, the catalytic asymmetric fluorination of 4-substituted pyrazolones remains highly desirable to give enantioenriched 4-fluoropyrazolones.

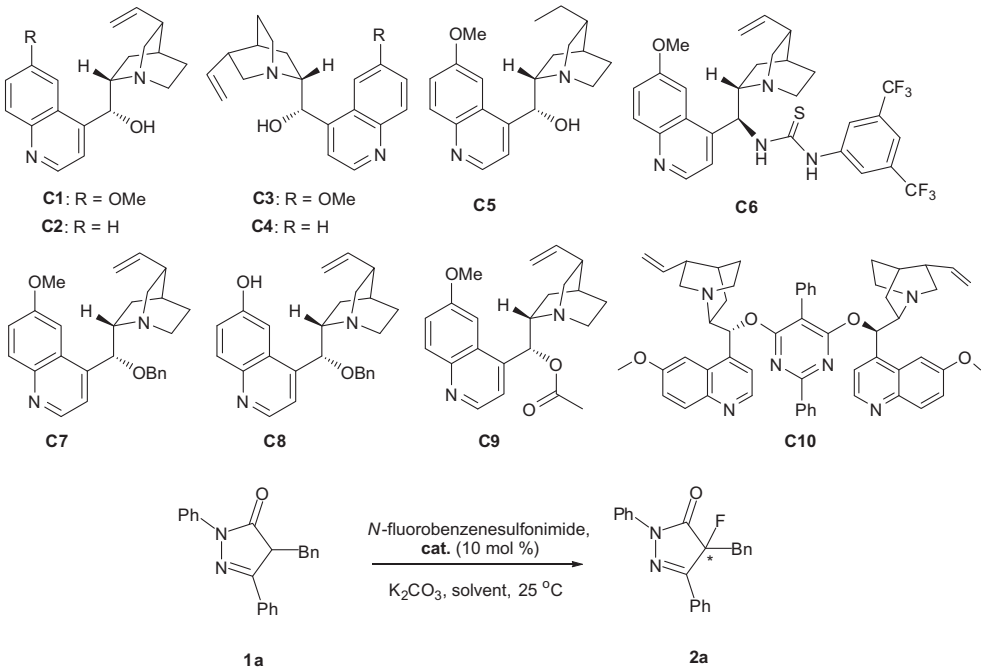
Herein we describe an enantioselective fluorination of 4-substituted pyrazolones with *N*-fluorobenzenesulfonimide catalyzed by cinchona alkaloids. The reactions proceeded smoothly to furnish various 4-fluoropyrazolones in excellent yields (up to 98%) and with moderate to good enantioselectivities (up to 81% *ee*).

2. Results and discussion

The fluorination of 4-substituted pyrazolone **1a** with *N*-fluorobenzenesulfonimide was selected as a model reaction to identify the optimal conditions (Table 1). With K_2CO_3 as the inorganic base and 10 mol % quinine **C1** as the catalyst, solvents were screened first. A brief survey of the medium disclosed that chlorinated solvent chloroform was the best choice to afford 27% *ee* and 90% yield (Table 1, entries 1–7). Considering our recent interests in pyrazolones and asymmetric fluorinations,[15] we paid attention to the evaluation of cinchona-based organocatalysts with chloroform as the solvent. Both cinchonidine **C2** and dihydroquinine **C5** afforded almost the same enantioselectivity (entries 8 and 11). The natural quinidine **C3** and cinchonine **C4** showed a decrease in enantioselectivity, with 23% *ee* and 18% *ee* (entries 9 and 10), respectively. These unsatisfactory results led us to the modification of quinine. The 9-thiourea modified cinchona alkaloid **C6**, enjoying great success in asymmetric organocatalysis, proved ineffective for enantioinduction in the current reaction (Table 1, entries 12). Unfortunately, the 9-OH modified catalyst **C7** and **C9** gave worse enantioselectivity (entries 13 and 15), with 15% *ee* and 17% *ee*, respectively. Thus, the 9-OH played a privileged role in chiral induction via hydrogen bonding with fluorinating reagent. The 6′-OH catalyst **C8** and bis-cinchona alkaloid **C10** were then examined, yet afforded poor enantiocontrol (entries 14 and 16).

The enantioselectivity with K_2CO_3 as the inorganic base could not be improved upon by varying the solvent or cinchona alkaloid. Thus, the screening of the inorganic bases was carried out to

Table 1
Screening of the chiral organocatalysts



Entry[a]	Cat.	Solvent	Time (h)	Yield (%)[b]	*ee* (%)[c]
1	**C1**	DCM	0.5	94	21
2	**C1**	$CHCl_3$	2	90	27
3	**C1**	DCE	4	84	15
4	**C1**	EtOAc	11	94	10
5	**C1**	Toluene	24	30	16
6	**C1**	Et_2O	22	87	18
7	**C1**	THF	24	87	14
8	**C2**	$CHCl_3$	2	90	26
9	**C3**	$CHCl_3$	2	96	−23
10	**C4**	$CHCl_3$	2	91	−18
11	**C5**	$CHCl_3$	3	95	26
12	**C6**	$CHCl_3$	1	94	6
13	**C7**	$CHCl_3$	1	95	15
14	**C8**	$CHCl_3$	15	93	16
15	**C9**	$CHCl_3$	1	94	−17
16	**C10**	$CHCl_3$	1.5	92	8

[a] Unless specified otherwise, reactions were carried out with **1a** (0.1 mmol), *N*-fluorobenzenesulfonimide (0.12 mmol), **C** (10 mol %) and K_2CO_3 (0.11 mmol) in solvent (1 mL) at 25 °C.
[b] Isolated yield.
[c] The *ee* values were determined by using chiral HPLC.