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Enantioselective Synthesis of Dihydrospiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] Derivatives via Michael/Hemiketalization Reaction

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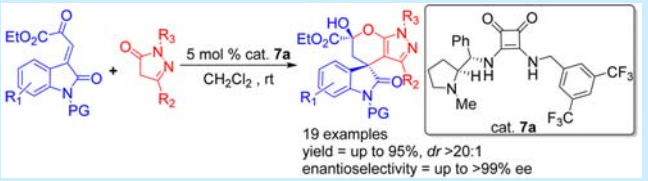
Supporting Information

ABSTRACT: A new bifunctional squaramide organocatalyst derived from L-proline mediated the first enantioselective synthesis of dihydrospiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivatives in excellent enantioselectivity by reacting pyrazolones with isatylidine β,γ-unsaturated α-ketoester. This new catalyst outperformed widely used thioureas and squaramides in inducing enantioselectivity.



The ever-growing need for new chemical entities is being met by organic chemists' efforts to synthesize novel chemical structures bearing various heterocycles.[1] Among the heterocycles, pyranopyrazoles have attracted the attention of synthetic chemists since they are a fertile source of biologically active molecules.[2] These motifs possess anticancer,[3] antimicrobial,[4] anti-inflammatory,[5] insecticidal,[6] and human Chk1 kinase inhibitory properties[7] act as biodegradable agrochemicals[8] (Figure 1). Because of the biological activity of pyranopyrazole,

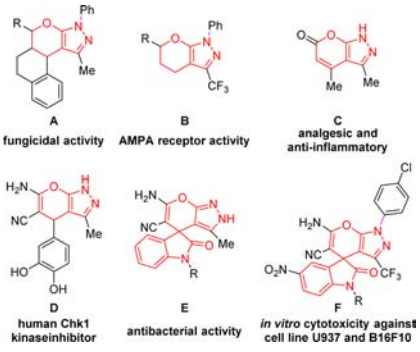


Figure 1. Biologically active pyrano[2,3-*c*]pyrazole compounds.

the synthesis of functionalized pyranopyrazole scaffolds is an important need in this decade.

In order to synthesize functionalized pyranopyrazoles, Erugu et al. reported the synthesis of spirooxindole fused with pyranopyrazoles.[9] These compounds exhibited anticancer activities (Figure 1). Similarly, other derivatives of pyrazoles with oxindoles possess anticancer activities.[10] However, since these compounds contain a chiral center, it is imperative to develop a methodology to yield these derivatives in an enantiomerically pure manner.

Li et al.[11a] and Gogoi et al.[11b] developed a Michael addition and a Thorpe−Ziegler type reaction, respectively, for the enantioselective synthesis dihydropyrano[2,3-*c*]pyrazoles. Ye and co-workers used NHC catalyst for the enantioselective [4 + 2] annulation of α-chloroaldehydes with pyrazolone-derived oxodienes to synthesize dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-ones.[12] An elegant approach by Enders and co-workers enabled one-pot asymmetric synthesis of tetrahydropyrano[2,3-*c*]pyrazoles.[13] Enantioselective annulation of pyrazolones with α,β-unsaturated aldehydes using base-free NHC catalysis resulted in the synthesis of dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one.[14]

Spirooxindoles motifs are widely embedded in many natural products and numerous pharmaceutical compounds that exhibit biological activities.[15] Assembly of the spirocyclic skeleton at the C-3 position of oxindole is known to enhance the biological activities of oxindole derivatives. The development of novel synthetic methodology for construction of spirooxindoles has continued to draw the attention of organic chemists. Recently, the organocatalytic cascade reactions provided access to spirooxindoles in a single step with high enantioselectivities.[16] Chen and co-workers demonstrated [3 + 2] annulation reaction of MBH carbonates derived from isatins with 1-azadienes to construct spirooxindoles in excellent enantioselectivities.[17a] Wu et al. shed light on assembly of spirooxindoles by organocatalytic multicomponent reactions using diazooxindole.[17b] NHC-catalyzed [3 + 2] annulation of aryl 3-bromoenals and isatins enabled the synthesis of spirooxindole−butenolide.[17c] Due to the importance and emergence of fused spirooxindoles, we are interested in synthesizing spirooxindoles fused with pyranopyrazoles. Despite the elegant methods noted in the literature to synthesize pyranopyrazoles, there is no enantioselective method to synthesize the spirooxindole-fused pyranopyrazoles.

Herein, we report the enantioselective synthesis of oxindoles fused with pyranopyrazoles using new bifunctional squaramide synthesized from L-proline. Our attempts began with the synthesis of dihydrospiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]

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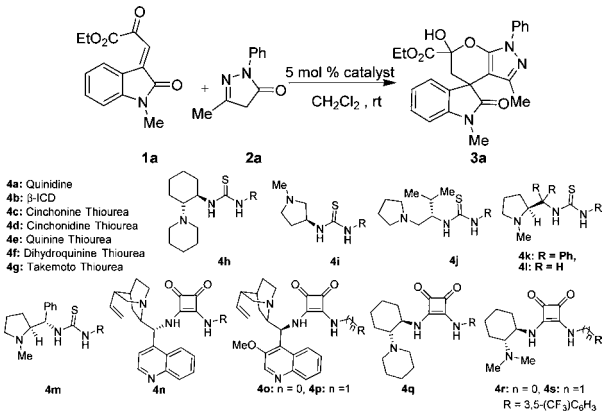
derivatives by treating ethyl (*E*)-3-(1-methyl-2-oxoindolin-3-ylidene)-2-oxopropanoate[18a] **1a** with pyrazolone **2a** using 5 mol % of quinidine **4a** as a catalyst in dichloromethane at ambient temperature. The reaction proceeded smoothly to afford a single diastereomer of the product **3a** in 82% yield with 22% enantioselectivity (Table 1, entry 1). Encouraged by these initial

Table 1. Catalyst Screening and Optimization of the Reaction Conditions[a]



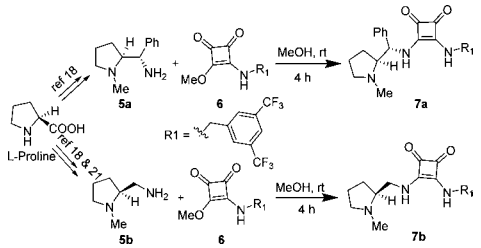
entry	catalyst	time (h)	yield (%)	ee[b] (%)
1	**4a**	2	82	−22
2	**4b**	1	87	8
3	**4c**	4	65	−55
4	**4d**	4	77	−78
5	**4e**	4	84	−47
6	**4f**	4	72	−66
7	**4g**	4	89	72
8	**4h**	4	75	58
9	**4i**	4	56	−49
10	**4j**	4	74	−76
11	**4k**	4	81	rac
12	**4l**	4	69	06
13	**4m**	4	91	88
14	**4n**	2	68	80
15	**4o**	2	86	75
16	**4p**	2	78	77
17	**4q**	2	81	53
18	**4r**	2	84	45
19	**4s**	2	79	40

[a]The reactions were carried out with **1** (0.193 mmol), **2** (0.193 mmol), and catalyst (0.0096 mmol) in 1 mL of CH_2Cl_2 at 25 °C to afford >20:1 dr of the product in all the cases. [b]Enantiomeric excess (ee) was determined by HPLC analysis using a chiral stationary phase. Minus sign indicates opposite diastereomer of the product compared to HPLC data.

results, we proceeded to optimize the reaction conditions by varying known organocatalysts **4b**−**k**. The observed results are depicted in Table 1 (entries 2−12). The yields and enantioselectivities of corresponding products were found to be moderate in all these experiments. These observations indicate that the construction of desired product **3a** could not be accomplished using commonly used organocatalysts. Our prior results motivated us to evaluate L-proline-derived thiourea[18] **4m** in this transformation. Although catalyst **4m** efficiently transformed substrates into the expected products in excellent yield and 88% of enantioselectivity, efforts to improve the enantioselectivity further did not bear any fruitful results.[19]

The recent successful use of squaramide organocatalysts and their ability to form stronger hydrogen bonds than thioureas motivated us to explore squaramides to improve the enantioselectivity further.[20] Similar to thioureas, squaramides represented in the recent literature were examined in the assembly of spirooxindole-fused pyranopyrazole **3a**. The results were not different from thiourea-mediated catalysis (**4n**−**s**). These unfruitful results intrigued us to turn our attention to synthesize strong hydrogen bond donor catalysts from L-proline (Scheme 1) since L-proline-derived thiourea **4m** provided the

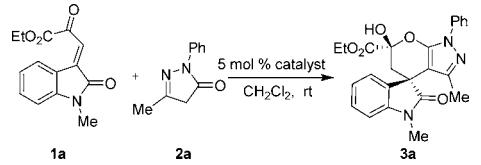
Scheme 1. Synthesis of L-Proline-Derived Bifunctional Squaramide



best outcome among the catalysts screened. We were delighted to observe that squaramide catalyst **7a** catalyzed the formation of product **3a** in excellent yield (95%) and enantioselectivity (99% ee).

To prove the necessity of the stereocenter at the carbon-bearing squaramide,[21] catalyst **7b**, which lacks a stereocenter, was also screened in the formation of product **3a**. The results indicate that without a stereocenter at carbon-bearing squaramide moiety there was no enantioselectivity (Table 2, entry 2). It is important

Table 2. Screening of Novel L-Proline-Derived Bifunctional Squaramides[a]



entry	catalyst	time (h)	yield (%)	ee[b] (%)
1	**7a**	**4**	**95**	**99**
2	**7b**	7	57	rac

[a]The reactions were carried out with **1** (0.193 mmol), **2** (0.193 mmol), and catalyst (0.0096 mmol) in 1 mL of CH_2Cl_2 at 25 °C to afford >20:1 dr of the product. [b]Enantiomeric excess (ee) was determined by HPLC analysis using a chiral stationary phase.

to note that the stereochemical outcome is effectively controlled by the newly generated stereocenter, which bears a squaramide moiety.

Thus, the first enantioselective synthesis of pyranopyrazole-fused oxindole was accomplished using a newly generated squaramide **7a** (5 mol %) synthesized from L-proline in dichloromethane at ambient temperature. Having achieved enantioselective synthesis of spirooxindole-fused pyranopyrazole,[19] the substrate scope of this reaction was undertaken.

First, the influence of N_1-protection of oxindole ketoester on enantioselectivity and yield was tested. It is evident that various N_1-substitutions like methyl, benzyl, allyl, and propargyl are well tolerated. The expected products **3a**−**d** were isolated in greater

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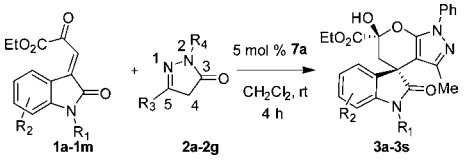
Table 3. Substrate Scope for the Michael/Hemiketalization Reaction[a]



entry	R_1, R_2	R_3, R_4	product	yield (%)	ee[b] (%)
1	Me, H **1a**	Me, Ph **2a**	**3a**	95	99
2	Bn, H **1b**	Me, Ph **2a**	**3b**	92	98
3	allyl, H **1c**	Me, Ph **2a**	**3c**	89	98
4	propargyl, H **1d**	Me, Ph **2a**	**3d**	91	98
5	H, H **1e**	Me, Ph **2a**	**3e**	86	96
6	Me, 5-F **1f**	Me, Ph **2a**	**3f**	87	96
7	Me, 5-Cl **1g**	Me, Ph **2a**	**3g**	85	90
8[c]	Me, 5-Br **1h**	Me, Ph **2a**	**3h**	89	>99
9	Me, 5-I **1i**	Me, Ph **2a**	**3i**	86	96
10	Me, 5-OMe **1j**	Me, Ph **2a**	**3j**	87	98
11	Me, 5-OCF_3 **1k**	Me, Ph **2a**	**3k**	90	97
12	Me, 7-F **1l**	Me, Ph **2a**	**3l**	83	96
13	Me, 5,7-Me **1m**	Me, Ph **2a**	**3m**	92	98
14	Me, H **1a**	CF_3, Ph **2b**	**3n**	82	90
15	Me, H **1a**	Ph, Ph **2c**	**3o**	84	95
16	Me, H **1a**	(4-OMe) C_6H_4,Ph **2d**	**3p**	80	94
17	Me, H **1a**	Ph, Me **2e**	**3q**	89	97
18	Me, H **1a**	Ph, H **2f**	**3r**	83	83
19	Me, H **1a**	Me, (2-F)C_6H_4 **2g**	**3s**	88	85

[a]The reactions were carried out with **1** (0.193 mmol), **2** (0.193 mmol), and catalyst **7a** (0.0096 mmol) in 1 mL of CH_2Cl_2 at 25 °C for 4 h to afford >20:1 dr of the products in all cases (^{1}H NMR). [b]Enantiomeric excess (ee) was determined by HPLC analysis using a chiral stationary phase. [c]CCDC no. 1415726.

than 89% yield and excellent enantioselectivity (Table 3, entries 1−4). Due to the strong hydrogen-bonding nature of squaramide, even there was no substitution on N_1-position, there was no diminished enantioselectivity (Table 3, entry 5). Pyrazolone **2a** was chosen as a model substrate to study the influence of various substituents on oxindole ketoester.

To our delight, various halogens and electron releasing and withdrawing substituents at the fifth position had very little influence on enantioselectivity (Table 3, entries 6−11). Variation on 7-substituted oxindole was also investigated. Gratifyingly, all these substrates underwent transformation to afford the corresponding pyranopyrazoles in excellent enantioselectivity (Table 3, entries 12 and 13). We subsequently studied the influence of differently substituted pyrazolones in the formation of spirooxindoles. The electronic properties of the substituents at C-5 position of pyrazolone seemed to have no influence either on the yield or enantioselectivity (Table 3, entries 14−16).

Replacement of phenyl substitution on N_2 of pyrazolones by methyl did not affect the enantioselectivity. The respected product **3q** was isolated in very good yield and excellent enantioselectivity (Table 2, entry 17). With no N_2 protection on the pyrazolone ring the reaction proceeded smoothly to afford the product **3r** in 83% enantioselectivity. The presence of electron-withdrawing fluoro substitution on the aryl ring at the N_2 position of pyrazole had little effect on the stereochemical outcome of the product (Table 3, entry 19). Thus, we developed an enantioselective assembly of spirooxindoles fused with functionalized pyranopyrazoles with wide substrate scope.

The absolute configuration of this reaction product **3h** was determined to be (7*S*,12*R*) by single-crystal X-ray analysis (Figure 2).[19]

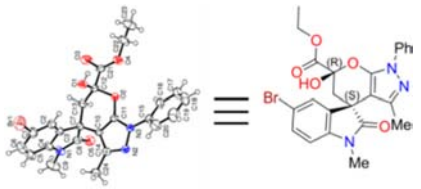


Figure 2. ORTEP diagram of the compound **3h**.

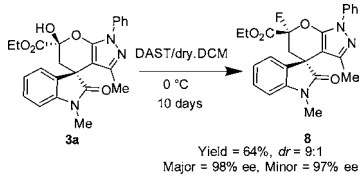
On the basis of the stereochemical outcome of this reaction, a plausible transition-state model is proposed to account for the formation of the major stereoisomer of the product **3h** via a Michael/hemiketalization pathway (Scheme 2).

Scheme 2. Plausible Transition-State Model of Michael/Hemiketalization Reaction

Oxindole ketoester **1a** interacts with the squaramide moiety of catalyst **7a** by two stronger hydrogen bonds.[20] The chiral tertiary amine part of catalyst **7a** deprotonates pyrazolone via tautomerization and provides steric bias for the approach of pyrazolone **2** to the oxindole ketoester **1**. The transition state formed by the dual activation facilitates the *Si*-face attack of pyrazolone **2a** to the oxindole ketoester **1a** followed by aromatization of pyrazolone and hemiketalization leading to the desired product **3a** in 4 h.

Replacing the hydroxyl group with a fluorine atom often enhances the safety and efficacy of drugs.[22] For the development of these fluorinated compounds, we explored fluorination of hemiketal product **3a** using fluorinating agent DAST (diethylaminosulfur trifluoride). Compound **3a** was treated with DAST in dichloromethane at 0 °C for 10 days to yield fluorinated product **8** (64%) with good diastereoselectivity and excellent enantioselectivity (Scheme 3). The stereochemistry of compound

Scheme 3. Synthesis of Biologically Active Fluorinated Compound



8 was assigned as the *R* configuration at the C−F stereocenter using ^{1}H NMR techniques.[19]

In conclusion, enantioselective synthesis of dihydrospiro-[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivatives using a new squaramide organocatalyst synthesized from L-proline was

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accomplished and reported for the first time. The new squaramide **7a** surpassed widely used thioureas and squaramides in yield and stereoselectivity with a broad range of substrate scopes under mild reaction conditions. The synthetic application of the Michael/hemiketalization product was explored by fluorination using fluorinating agent DAST in good diastereoselectivity (9:1) and excellent enantioselectivity (major isomer 98% ee and minor isomer 97% ee). Investigation of these derivatives in biological targets is being pursued in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00287.

Experimental procedure, compound characterization data, ^{1}H and ^{13}C NMR spectra, and crystallographic data (PDF)
Crystallographic data for compound **3h** (CIF)

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Notes

The authors declare no competing financial interest.

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