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Enantioselective access to tetrahydropyrano[2,3-*c*]pyrazoles *via* an organocatalytic domino Michael-hydroalkoxylation reaction

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ABSTRACT

An asymmetric domino Michael-hydroalkoxylation reaction of *trans*-α-alkynyl-nitroolefins with *N*-arylpyrazolinones has been accomplished using a chiral bifunctional squaramide catalyst. Under the organocatalytic method, a broad range of tetrahydropyrano[2,3-*c*]pyrazoles with an exocyclic alkene at the C-6 position were prepared in high yields and excellent stereoselectivities. The presence of an exocyclic double bond and nitro group in the pyranopyrazoles provide a wide scope for further structural transformations.

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Pyranopyrazoles are ubiquitous motifs in numerous heterocyclic molecules with impressive biological activities;[1] selected examples are shown in Fig. 1. For instance, pyranopyrazol-6-one derivative **A** possesses analgesic and anti-inflammatory properties,[2] compound **B** enhances the AMPA receptor activity,[3] and molecules of type **C** are known fungicides.[4] In addition, several chiral pyrano-annulated pyrazoles exhibit a wide range of therapeutic properties including antimicrobial,[5] antitubercular,[6] antibacterial[7] and human Chk1 kinase inhibitory properties.[8]

Due to their extensive medicinal relevance, pyrano-annulated pyrazole scaffolds featuring multiple stereogenic centers have emerged as appealing synthetic targets in recent years. As a consequence, a number of elegant strategies have been established to construct these skeletons. For example, one-pot syntheses of pyranopyrazoles have been reported employing pyrazolinones and α,β-unsaturated aldehydes/ketones through iminium catalysis.[9] Similar structures have also been prepared *via* NHC organocatalysis.[10] Tetrahydropyranopyrazoles (THPPs) with three consecutive stereogenic centers have been synthesized using electrophilic alkylidene pyrazolinones.[11] A few other organocatalytic methods reported for the synthesis of THPPs and dihydropyranopyrazoles (DHPPs) include Michael/Thorpe-Ziegler type reaction,[12] Michael/ hemiketalization,[13] and formal [3+3] annulations.[14]

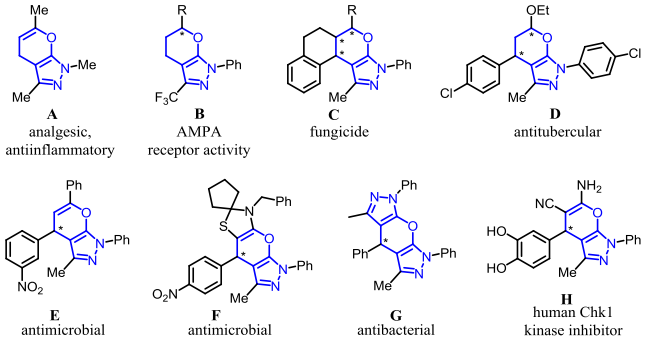

Fig. 1. Selected examples of biologically important pyranopyrazoles.

Recently, a sequential approach involving a combination of metal and organocatalysis for the synthesis of DHPPs has been described by Enders and co-workers (Scheme 1).[15]

Although many efficient asymmetric methods to furnish pyrano-annulated pyrazoles and spyro-pyrazolinones[16] have been achieved to date, domino reactions employing a bielectrophile α-alkynyl-nitroolefin[17] to enantioselectively construct THPPs remains unknown. As a part of our research interest in developing novel and facile methods to produce architecturally interesting and bioactive molecules,[18] we became interested in the asymmetric synthesis of more versatile THPPs with an exocyclic alkene, an important functionality for further structural manipulation. It

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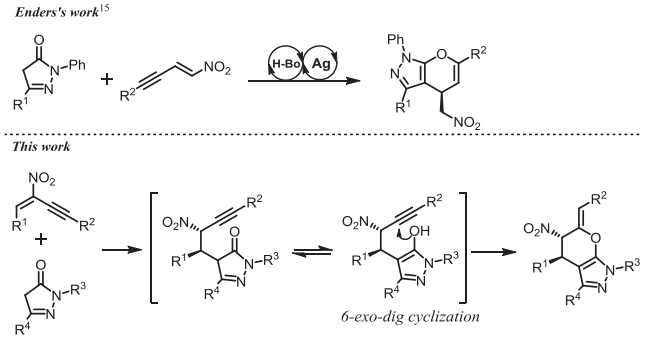


Scheme 1. Asymmetric synthesis of pyranopyrazoles.

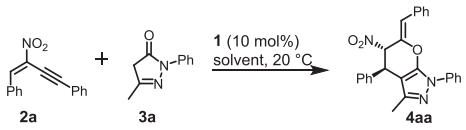
was envisioned that an ambident nucleophilic pyrazolinone[19] would undergo asymmetric Michael reaction with the α-alkynylnitroolefin in the presence of a bifunctional organocatalyst,[20] and re-aromatization of the pyrazolinone unit followed by *6-exo-dig* cyclization of the Michael intermediate thereafter would produce the THPP derivative (Scheme 1).

While our work was in progress, Tsai, Chen and co-workers disclosed a sequential approach for the synthesis of (*Z*)-2-methylenepyrans *via* allene formation/oxa-Michael/alkene isomerization reactions.[21] Very recently, Xu and co-workers explored 1,3-enynes in an organocatalytic one-pot Friedel–Crafts alkylation/annulation/nitro-Michael reaction for the synthesis of chroman derivatives.[22] Herein, we report an efficient enantioselective synthesis of tetrahydropyrano[2,3-*c*]pyrazoles through a domino Michael-hydroalkoxylation reaction, using a cinchona derived squaramide organocatalyst.

At the outset, the reaction between *trans*-α-phenylethynylnitrostyrene **2a** and *N*-phenylpyrazolinone **3a** was examined in the presence of *Cinchonidine* **1a** (10 mol%) in toluene at 20 °C. We were delighted to observe the formation of desired pyrano-annulated pyrazole **4aa** (48% yield, 27% ee), predominantly as the *Z*-isomer through a Michael addition followed by *6-exo-dig* cyclization (Table 1, entry 1).

To optimize the domino reaction, several other *Cinchona* alkaloids and their derivatives were evaluated as bifunctional organocatalysts (Fig. 2). It was observed that thioureas **1e–g** improved the reaction yield to some extent (Table 1, entries 5–7). Gratifyingly, *Cinchona*-derived squaramides **1h** and **1i**, gave pyranopyrazole **4aa** in 70%, 68% yield and 88%, 82% ee, respectively (Entries 8 and 9). Thus, it was quite clear that catalysts with the squaramide unit (**1h–i**) were superior over the thioureas (**1e–g**) in terms of chemical yield as well as optical yield. Interestingly, cyclohexanediamine-derived squaramide **1j** also catalyzed the domino reaction to give the product in moderate yield with very good enantiopurity (86% ee). Among the examined catalysts, *Cinchonidine*-derived squaramide **1h** was the best in terms of chemical and optical yields. Upon lowering the catalyst loading

Table 1
Optimization of reaction conditions.[a]



Entry	1	Solvent	Time (h)	*Z*:*E*[b]	Yield[c] (%)	*ee*[d] (%)
1	**1a**	Toluene	36	9:1	48	27
2	**1b**	Toluene	36	9:1	40	20
3	**1c**	Toluene	36	9:1	44	23
4	**1d**	Toluene	36	9:1	42	15
5	**1e**	Toluene	24	16:1	60	16
6	**1f**	Toluene	24	15:1	56	10
7	**1g**	Toluene	24	16:1	58	20
8	**1h**	Toluene	16	25:1	70	88
9	**1i**	Toluene	16	25:1	68	82
10	**1j**	Toluene	16	15:1	66	86
11[e]	**1h**	Toluene	40	20:1	65	88
12[f]	**1h**	Toluene	40	15:1	52	88
13[g]	**1h**	Toluene	36	15:1	46	88
14[h]	**1h**	Toluene	36	12:1	23	87
15	**1h**	$PhCF_3$	16	20:1	64	85
16	**1h**	$CHCl_3$	14	25:1	69	93
17	**1h**	CH_2Cl_2	14	25:1	72	96
18	**1h**	DCE	14	25:1	70	93
19	**1h**	CH_3CN	20	20:1	58	83
20	**1h**	THF	20	20:1	55	78
21[i]	**1h**	CH_2Cl_2	14	>30:1	78	96

[a] Reaction conditions: **2a** (0.20 mmol), **3a** (0.24 mmol), **1** (0.02 mmol), solvent (1 mL), 20 °C, unless specified.
[b] Determined by ^1H NMR analysis of crude reaction mixture.
[c] Isolated yield of **4aa** (*Z*-isomer).
[d] Determined by chiral HPLC analysis.
[e] 5 mol% catalyst **1h**.
[f] 2 mol% catalyst **1h**.
[g] Reaction conducted at 10 °C.
[h] Reaction conducted at 0 °C.
[i] Reaction conducted at 30 °C.

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