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Asymmetric Synthesis of Spiro[chroman-3,3'-pyrazol] Scaffolds with an All-carbon Quaternary Stereocenter *via* a *oxa*-Michael-Michael Cascade Strategy with Bifunctional Amine-thiourea Organocatalysts

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An efficient chiral bifunctional amine-thiourea catalysed cascade *oxa*-Michael-Michael addition of 4-alkenyl pyrazolin-3-ones to (*E*)-2-(2-nitrovinyl)phenol for the synthesis of chiral heterocyclic systems containing spiro[chroman-3,3'-pyrazol] scaffolds has been developed. This reaction afforded the desired products in high to excellent yields (up to 98%) with moderate to high enantioselectivities (up to 99%) and diastereoselectivities (up to 20:1) under low catalyst (15 mol%). This catalytic asymmetric reaction provides an efficient route toward the synthesis of chiral spiro[chroman-3,3'-pyrazol] derivatives containing three contiguous stereocenters which possess potential pharmaceutical activities.

Chromanes and dinitrogen-containing heterocycles are important core structure found in natural products and biologically active molecules (Fig. 1).[1] Furthermore, some sophisticated structures in which heterocycle core spiro-fused with a chroman moiety were found in many biologically active natural or synthetic products.[2] Therefore, the development of novel catalytic asymmetric methods for the efficient construction of structurally diverse and densely functionalized spirohetero-cycle-chroman compounds have been extensively studied.[3] For example, Rapposelli reported the synthesis of 4-spiro-oxazolidinone-benzopyran derivatives as aldose reductase inhibitors.[3b] Very recently, Zhu reported the highly stereoselective synthesis of indolinones spiro-fused with chromans or tetrahydroquinolines through a chiral amine-catalyzed *oxa*- and *aza*-Michael-Michael cascade methodology.[3e] However, there is no suitable asymmetric method to prepare spiro-chroman-pyrazol derivatives in enantiomerically pure form with more functional diversity.

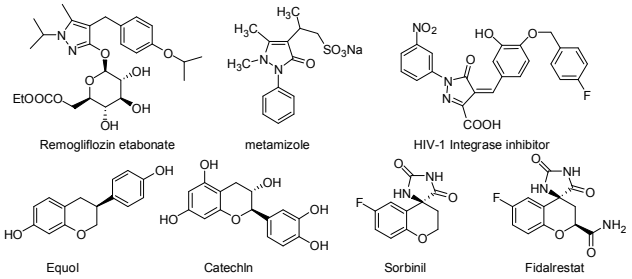

Figure 1. Representative examples of biologically active pyrazolone derivatives and chroman derivatives.

The organocatalytic asymmetric formation of highly enantiopure compounds represents an increasingly important field in organic chemistry. Many natural products and biologically interesting compounds have been successfully synthesized based on this synthetic strategy.[4] Moreover, organocatalytic cascade reactions avoid time-consuming and costly protection/deprotection processes as well as the purification of intermediates. They often proceed with excellent stereoselectivities and increase molecular complexity.[5] Therefore, organocatalytic domino reactions has been demonstrated as an effective tool in contemporary organic synthesis. Recently, in order to access chiral chroman cores, organocatalytic Michael/hemiacetalization cascade reaction was envisaged using aldehydes and (*E*)-2-(2-nitrovinyl) phenols as substrates.[3b-d,6] However, there are no chiral Lewis base catalyzed *oxa*-Michael-Michael cascade reactions to prepare spirodihydrocoumarins in enantiomerically pure form with more functional diversity. Inspired by the work of Zhu on the use of squaramide-tertiary amine-hydrogen-bond donor catalysts in asymmetric domino reactions with the construction of spiro[chroman-3,3'-oxindole] skeletons, herein, we described our results on chiral Lewis base catalyzed *oxa*-Michael-Michael cascade sequences between 4-benzylidene-5-methyl-2-phenylpyrazolone and (*E*)-2-(2-nitrovinyl) phenols.

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This methodology permits production of spiro[chroman-3,3'-oxindole] derivatives with an all-carbon quaternary stereocenter[7] and the spirane system[8] and provides the product in excellent yields and stereoselectivities with up to >20:1 diastereomeric ratio (*dr*) and 99% enantiomeric excess (*ee*).

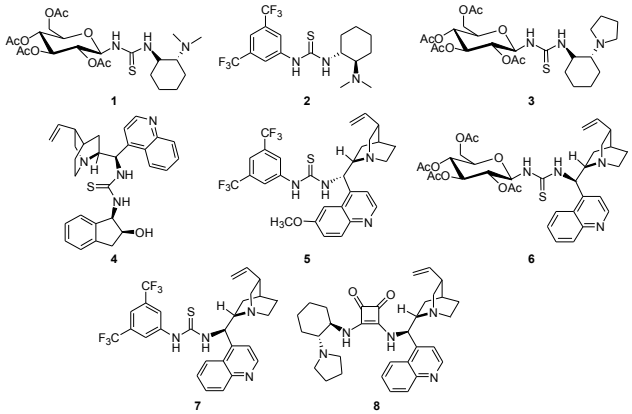


Figure 2. Catalyst structures.

A series of readily available thiourea and squaramide organocatalysts **1**-**8** (Fig. 2) were synthesized according to previous reports.[9] We initially investigated the *oxa*-Michael-Michael reaction between (*E*)-2-(2-nitrovinyl)phenol **9a** and 4-benzylidene-5-methyl-2-phenylpyrazolone **10a** by the action of 15 mol% of organocatalysts **1**-**7** in toluene as solvent at 0 ºC. The results are presented in Table 1. It was found that the catalyst structures have remarkable effects on the stereochemical results. Catalyst **1** could catalyse this reaction to provide the desired product **11a** with moderate enantioselectivity (78% *ee*) but poor diastereoselectivity (63:37 *Dr*) in excellent yield (Table 1, entry 1). Next, the Takemoto bifunctional thiourea catalyst **2** was tested, which has been reported to give very good results in the enantioselective Michael addition of malonates to nitroalkenes.[10] In our protocol, **11a** was formed in good yield with good enantioselectivity, but again with only a poor *Dr* value (Table 1, entry 2).

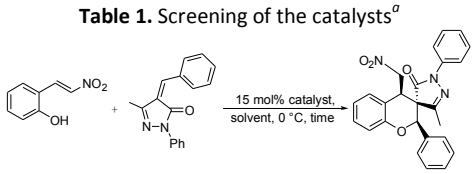
Further investigations showed that the catalyst **3** gave better diastereoselectivity control for the desired product compared to the bifunctional indane catalyst **4** (Table 1, entries 3-4). Next, we explored the 3,5-bis(trifluoromethyl)phenyl thiourea **5** and cinchona-based thioureas **6** and **7** as catalysts, and found that the desired products were obtained in yields of 80-95% with the opposite sense moderate *ee* values of 34-79% and bad *Dr* values (Table 1, entries 5-7). Thiourea organocatalysts **1**-**7** did not give a higher diastereoselectivities. We then tried to use four squaramide-cinchona bifunctional catalyst **8** derived from (1*S*,2*S*)-cyclohexane-1,2-diamine and cinchonine in this reaction. However, the squaramide **8** also did not perform better than thiourea **1**-**7** (Table 1, entry 8). From this comparative study, the bifunctional thiourea **3** was the best choice as an organocatalyst because of its stereoselectivity and efficiency.

With carbohydrate/cyclohexane-1,2-diamine thiourea **3** as the best catalyst, we further screened the effect of solvents, catalyst loading, and temperature for the optimal reaction conditions. Among the solvents used, dichloromethane, chloform, MTBE and Et_2O, usually good solvent for thiourea-amine catalyzed reactions, led to moderate to excellent yields and enantioselectivities (Table 1, entries 9-12). Aprotic polar solvents such as MeCN and EtOAc were suitable for this reaction with respect to the reaction time and enantioselectivities results (Table 1, entries 13-14). The reaction could also be performed in protic polar solvent like MeOH, but again poor stereoselectivity was obtained (Table 1, entry 15). The screening of solvents identified MeCN as the optimal solvent for this reaction. Then the catalyst loading was decreased, and we found that decreasing the catalyst loading could lead to the decrease of the enantioselectivity and yield (Table 1, entry 16), while the high enantioselectivity was still maintained with an increased catalyst loading from 15 to 20 mol%, and excellent yield was obtained at the mean time (Table 1, entry 17). When the reaction was carried out at -20 ºC in MeCN using **3** as the catalyst, a lower enantiomeric excess value of 90% with 85% yield was obtained (Table 1, entry 18).

To further increase the reaction diastereo- and enantioselectivity, the effect of additives was investigated (Table 2). A survey of different acidic additives revealed that an acidic additive was necessary to the catalyst system to achieve high catalytic performance. In our investigation, the beneficial effects of glycine and aspartic acid were observed (Table 2, entries 1-2). After screening different kinds of aromatic acid compounds (Table 2, entry 3-10), it was found that benzene-sulfonic acid (BSA) gave superior results in terms of reactivity and stereoselectivity (Table 2, entry 10). To further optimize the catalytic system to achieve higher *Dr*, 4Å molecular sieves (M.S.) were therefore added, the reaction was completed with the same conversion and slightly increased *Dr* value within 24h (Table 2, entry 11). Decreasing the additive BSA/catalyst **3** molar ratio to 0.5:1 resulted in lower conversion (90%) and *ee* (93%) and lower *Dr* (71:29) in 48h (Table 2, entry 12). Further reduction in the amount of catalyst loading to 10 mol% prolonged the reaction time with no positive change in both diastereo- and enantioselectivity

(Table 2, entry 13). Thus, the optimal reaction conditions for this transformation were determined to be 0.5 mmol (*E*)-2-(2-nitrovinyl)phenols **9** 1.2 equivalents of 4-benzylidene-5-methyl-2-phenylpyrazolone **10**, 15 mol% of catalyst **3** combined with 15 mol% of BSA in 2 mL CH_3CN with 4Å MS (50 mg) at 0 ºC.

Table 1. Screening of the catalysts[a]

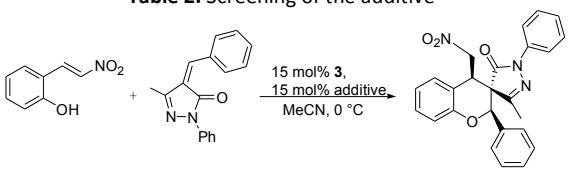


9a 10a 11a

Entry	Catalyst	Solvent	Time (h)	*Dr*[b]	*ee* (%)[c]	Yield (%)[d]
1	**1**	$PhCH_3$	15	63:37	78	99
2	**2**	$PhCH_3$	15	63:37	92	99
3	**3**	$PhCH_3$	15	68:32	94	96
4	**4**	$PhCH_3$	72	—	—	<10
5	**5**	$PhCH_3$	24	33:67	-57	80
6	**6**	$PhCH_3$	15	19:81	-79	95
7	**7**	$PhCH_3$	15	18:82	-34	83
8	**8**	$PhCH_3$	72	16:84	-38	68
9	**3**	CH_2Cl_2	48	26:74	-54	81
10	**3**	$CHCl_3$	12	64:36	93	93
11	**3**	MTBE[e]	48	63:37	92	75
12	**3**	Et_2O	36	69:31	94	93
13	**3**	MeCN	24	63:37	94	99
14	**3**	AcOEt	24	67:33	93	99
15	**3**	MeOH	48	30:70	-20	70
16[f]	**3**	MeCN	48	71:29	93	90
17[g]	**3**	MeCN	24	67:33	94	92
18[h]	**3**	MeCN	48	60:40	90	85

[a] Unless otherwise specified, all reactions were carried out using (*E*)-2-(2-nitrovinyl)phenol **9a** (0.5 mmol, 1 equiv) and 4-benzylidene-5-methyl-2-phenylpyrazolone **10a** (0.6 mmol, 1.2 equiv) in 2 mL solvent with 15 mol% of catalyst at 0°C. [b] Diastereomeric ratio (*Dr*) values were determined by ^{1}H NMR of unpurified products. [c] *ee* values of the major diastereoisomer were determined by chiral HPLC analysis. [d] Yield of isolated product of **11a** after column chromatography. [e] MTBE = methyl tertbutyl ether. [f] 10 mol% of catalyst **3** was used. [g] 20 mol% of catalyst **3** was used. [h] The reaction was performed at -20°C.

Table 2. Screening of the additive[a]



9a 10a 11a

Entry	Additive	Time (h)	*Dr*[b]	*ee* (%)[c]	Yield (%)[d]
1	Glycine	24	68:32	93	99
2	Aspartic acid	24	68:32	93	98
3	$PhCO_2H$	48	76:24	93	99
4	BTFMBA[e]	24	74:26	94	99
5	*p*-Cl-$PhCO_2H$	24	72:28	93	99
6	*o*-OCH_3-$PhCO_2H$	48	76:24	93	99
7	*p*-NH_2-$PhCO_2H$	48	75:25	93	85
8	*o*-CH_3-$PhCO_2H$	24	77:23	92	98
9	PTSA[f]	48	76:24	95	58
10	BSA[g]	48	79:21	94	99
11[h]	BSA	24	80:20	95	99
12[i]	BSA	48	71:29	93	90
13[j]	BSA	60	72:28	90	92

[a] Reactions were carried out on a 0.5 mmol scale with 1.2 equiv of **10a** in 2 mL of MeCN. [b] Diastereomeric ratio (*Dr*) values were determined by ^{1}H NMR of unpurified products. [c] *ee* values of the major diastereoisomer were determined by chiral HPLC analysis. [d] Yield of isolated product of **11a** after column chromatography. [e] BTFMBA = 3,5-bis (trifluoromethyl) benzoic acid. [f] PTSA = *p*-toluene sulfonic acid. [g] BSA = benzene sulfonic acid. [h] 4Å MS is added (50 mg). [i] BSA/catalyst **3** molar ratio is 0.5:1. [j] 10 mol% of catalyst **3** and additive were used.

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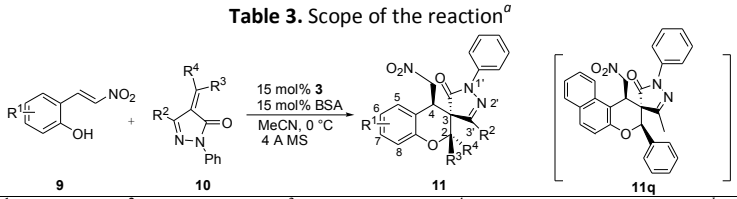
Using these optimized reaction conditions, we then examined the scope and limitations of the bifunctional amine-thiourea organocatalyzed *oxa*-Michael-Michael cascade reaction between (*E*)-2-(2-nitrovinyl) phenols **9** and different pyrazolone derivatives **10**, and the results are shown in Table 3. In the cases of pyrazolone derivatives bearing an electron-withdrawing or -donating group at the *ortho*, *meta* or *para* position of the benzene ring with (*E*)-2-(2-nitrovinyl)phenols **9**, the reactions were complete after 24-36h furnishing the products **11a-k** in excellent yields (95-99%), moderate diastereoselectivities (*dr*: 68:32-80:20) and excellent enantiomeric excesses (*ee*: 85 to 98%) (Table 3, entries 1-11). We were delighted to find that pyrazolone derivatives bearing furyl group underwent smooth cascade reaction with **9a** to give the corresponding product **11l** in 73% yield and moderate enantioselectivity (*ee* 86%) but bad diastereomeric ratio (*Dr*: 54:46) (Table 3, entry 12).

When 4-isopyropylidene-5-methyl-2-phenyl pyrazolone was used as the donor, the product was obtained in a virtually diastereo- and enantiomerically pure form (*Dr*: 93:7, *ee* > 99%) with excellent yield (97%) (Table 3, entry 13). The bulkier pyrazolone derivative was also suitable substrate, and its reaction was complete in 24h; however, it provided inferior stereoselectivity and lower yield (Table 3, entry 14). Next, we reacted 4-benzylidene-5-methyl-2-phenylpyrazolone with several substituted (*E*)-2-(2-nitrovinyl) phenols **9**. Most reactions could complete at 0 ºC affording the desired spiro[chroman-3,3'-pyrazol] derivatives **11** in moderate to satisfying yields, and some of them exhibited good to excellent diastereo- and enantioselectivities. These reactions could tolerate an electron-withdrawing or -donating group at *meta* or *para* position of the benzene ring of compound **9**, although the reactions of these substituted (*E*)-2-(2-nitrovinyl)phenols proceeded more slowly (Table 3, entries 15-18). Alternative of **10t** with **10s** did not significantly affect the reaction, giving corresponding product **11t** in good yield and stereoselectivity (Table 3, entries 19-20). The relative and absolute configurations of the title compounds were determined to be (*R*,*R*,*R*) by means of single crystal X-ray diffraction **11a** (Fig. 3).[11]

Table 3. Scope of the reaction[a]



Entry	Product	R^1	R^2	R^3	R^4	Time (h)	*Dr*[b]	*ee* (%)[c]	Yield (%)[d]
1	**11a**	H	Me	C_6H_5 (**10a**)	H	24	80:20	95	99
2	**11b**	H	Me	*o*-FC_6H_4 (**10b**)	H	24	76:24	92	95
3	**11c**	H	Me	*p*-FC_6H_4 (**10c**)	H	36	70:30	91	99
4	**11d**	H	Me	*o*-ClC_6H_4 (**10d**)	H	36	72:28	85	99
5	**11e**	H	Me	*m*-ClC_6H_4 (**10e**)	H	36	74:26	96	97
6	**11f**	H	Me	*p*-ClC_6H_4 (**10f**)	H	36	71:29	98	99
7	**11g**	H	Me	*m*-BrC_6H_4 (**10g**)	H	24	70:30	94	99
8	**11h**	H	Me	*p*-BrC_6H_4 (**10h**)	H	24	72:28	98	99
9	**11i**	H	Me	*m*-MeC_6H_4 (**10i**)	H	24	75:25	98	99
10	**11j**	H	Me	*p*-MeC_6H_4 (**10j**)	H	24	76:24	96	99
11	**11k**	H	Me	*m*-$NO_2C_6H_4$ (**10k**)	H	20	68:32	94	97
12	**11l**	H	Me	furyl (**10l**)	H	72	54:46	86	73
13	**11m**	H	Me	CH_3 (**10m**)	CH_3	36	93:7	>99	97
14	**11n**	H	C_6H_5	C_6H_5 (**10n**)	H	24	70:30	83	87
15	**11o**	6-Br	Me	C_6H_5	H	48	75:25	96	87
16	**11p**	6-NO_2	Me	C_6H_5	H	72	>20:1	70	83
17	**11q**	5,6-C_4H_4	Me	C_6H_5	H	72	>20:1	87	88
18	**11r**	6,8-$C(CH_3)_3$	Me	C_6H_5	H	24	62:38	94	99
19	**11s**	7-MeO	Me	*p*-ClC_6H_4 (**10f**)	H	72	85:15	64	89
20	**11t**	7-MeO	Me	*p*-MeC_6H_4 (**10j**)	H	72	80:20	98	90

[a] Reaction conditions: (*E*)-2-(2-nitrovinyl)phenols **9** (0.5 mmol), 4-benzylidene-5-methyl-2-phenylpyrazolone **10** (0.6 mmol), in 2 mL of MeCN at 0 °C in the presence of 15 mol% of catalyst **3** and 15 mol% BSA as additive with 4Å MS (50 mg). [b] Diastereomeric ratio (*Dr*) values were determined by ^{1}H NMR of unpurified products. [c] *ee* values of the major diastereoisomer were determined by chiral HPLC analysis. [d] Isolated yield after silica gel chromatography of **11**.

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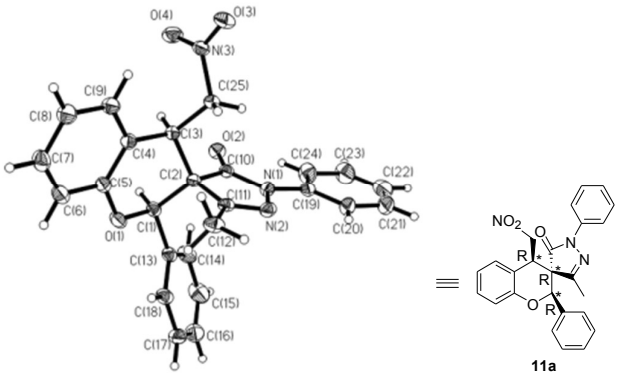
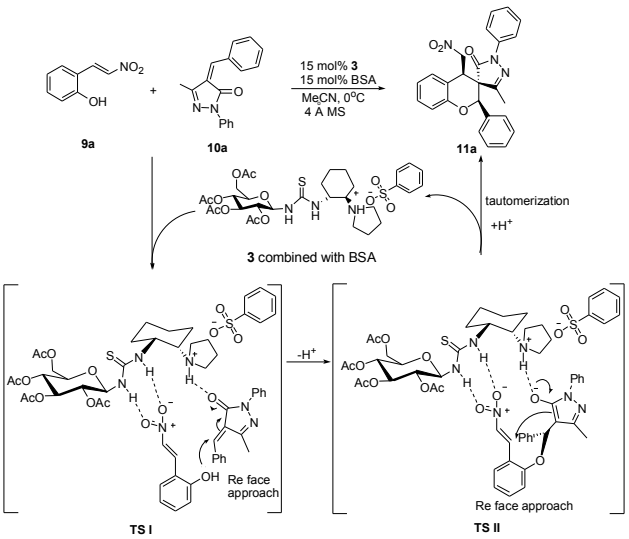


Figure 3. X-ray crystal structure of **11a**.



Scheme 1. Proposed reaction mechanism.

The possible mechanism for the reaction is shown in Scheme 1. In the transition state I (TS I) (*E*)-2-(2-nitrovinyl)phenol **9a** is activated by the thiourea moiety of bifunctional catalyst **3** through double hydrogen bonding between the NH groups and the nitro group while the neighboring tertiary amine activates 4-benzylidene-5-methyl-2-phenyl pyrazolone **10a**. The hydroxy group of (*E*)-2-(2-nitrovinyl)phenol **9a** would trigger a cascade sequence by the intermolecular *oxa*-Michael addition of oxygen to pyrazolone through *Re*-face attack to give the postulated TS II, followed by the intramolecular Michael addition through *Re*-face attack. Finally, tautomerization yielded the desired product **11a** with the release of catalyst **3**. The mechanism indicates that the thiourea moiety and cyclohexyl scaffold of the bifunctional catalyst play a significant role in controlling the stereoselectivity of the *oxa*-Michael-Michael cascade reaction.

Conclusions

In conclusion, we have developed a convenient and efficient organocatalytic cascade *oxa*-Michael-Michael reaction of 2-hydroxynitrostyrenes with pyrazolone derivatives for the asymmetric synthesis of spiro[chroman-3,3'-pyrazol]skeletons. This protocol proceeded well under mild conditions to furnish a series of spiro[chroman-3,3'-pyrazol] derivatives containing three contiguous stereocenters, including one spiro quaternary chiral center in good to excellent yields, moderate to excellent diastereoselectivities, and high to excellent enantioselectivities. Further studies on the asymmetric synthesis of related spirocyclic compounds catalyzed by organocatalysts are currently underway in our laboratory.

Acknowledgements

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11 Crystallographic data for the structural analysis of compound **11a** has been deposited at the Cambridge Crystallographic Data Centre as No. **CCDC** 1428773. These data can be obtained free of charge by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk.