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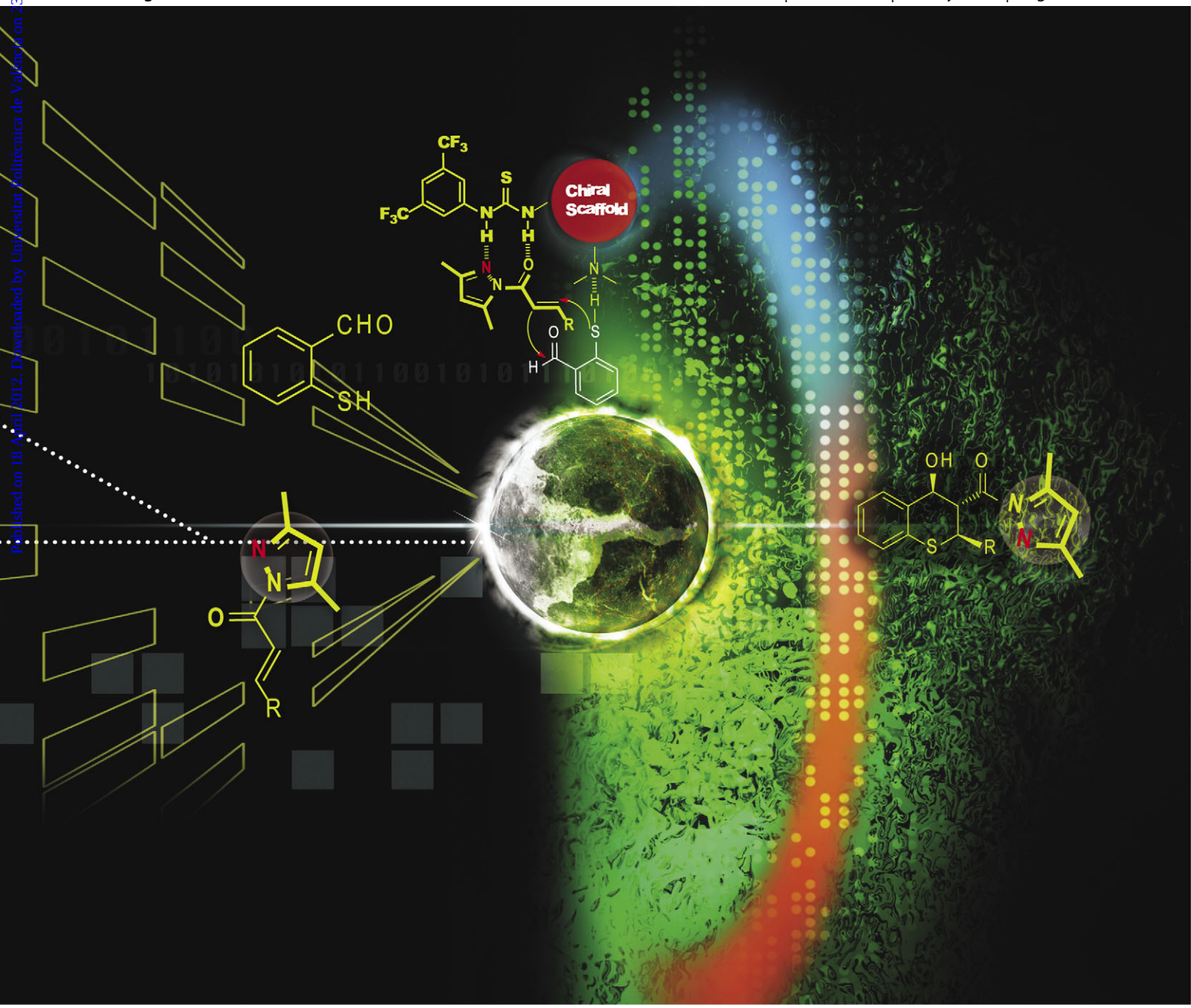

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Organocatalytic asymmetric domino sulfa-Michael–aldol reactions of 2-mercaptobenzaldehyde with α,β-unsaturated *N*-acylpyrazoles for the construction of thiochromane†

Xiu-Qin Dong,‡[a] Xin Fang,‡[a] Hai-Yan Tao,[a] Xiang Zhou[a] and Chun-Jiang Wang*[ab]

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An efficient protocol for the direct construction of bioactive thiochromanes was developed *via* a catalytic asymmetric cascade sulfa-Michael–aldol reaction of 2-mercaptobenzaldehyde with α,β-unsaturated *N*-acyl imides. The key to the present methodology is introducing a pyrazole moiety as H-bond acceptor, which allowed for better organization and activation and hence higher enantioselectivity.

Optically active chiral sulfur-containing compounds have important applications in many areas of chemistry and biology, for example, serving as antibiotics, as ligands or catalysts, and as chiral auxiliaries.[1] Highly functionalized thiochromanes, the sulfur analogues of chromanes, are common structural motifs in many pharmaceutical molecules and have been reported to possess important biological activities.[2] Some representative examples are shown in Fig. 1. Thiochromane derivative **A** displays high clinical efficacy in tamoxifen and fulvestrant resistant ER-positive breast cancer patients.[3] Compound **B** exhibited potent anti-HIV activity.[4] Compound **C** showed a mixed binding affinity to dopamine D_2, D_3 and $5HT_{A1}$ receptors,[5] whereas tertatolol **D** and its analogue **E** were revealed to be $5HT_{1A}$ receptor agonists for use in depression, schizophrenia and Parkinson's disease.[6]

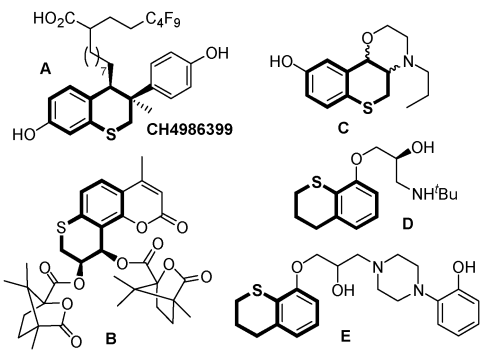

Fig. 1 Examples of biologically active thiochromane derivatives.

Owing to their biological relevance, several asymmetric methods have been developed for the facile access to such compounds.[7] Recently, Wang and co-workers reported an elegant approach to the highly functionalized thiochromane derivatives with excellent diastereoselectivity and enantioselectivity control *via* an organocatalyzed cascade Michael–aldol reaction of 2-mercaptobenzaldehydes with α,β-unsaturated oxazolidineones.[7b] In spite of the considerable advancements, the electron-deficient alkene substrates are limited to β-aryl substituted α,β-unsaturated oxazolidineones. Most recently, we have developed a new and efficient protocol for the organocatalytic asymmetric sulfa-Michael addition of thiols to easily-available (*E*)-4,4,4-trifluoro-crotonoyl-pyrazole,[8] which overcomes the drawback of our previous work employing expensive (*Z*)-ethyl 4,4,4-trifluoro-crotonate as the Michael acceptor,[9] in which the pyrazole moiety[10] was revealed to play a key role in providing H-bond acceptor sites for better chelation and hence accelerating reactions and improving enantioselectivities. Encouraged by these achievements and stimulated by the biological significance of the thiochromane derivatives,[2] we envisioned that switching the amide motif of unsaturated *N*-acylimide from oxazolidineone to pyrazole might improve its stereoselectivity control for the above-mentioned cascade sulfa-Michael–aldol reaction. Herein, we report our investigations on the use of *N*-acyl pyrazoles as H-bond accepters, providing diverse thiochromanes with excellent stereoselectivities for both β-aryl and β-alkyl substituted α,β-unsaturated *N*-acylimides.

To explore the feasibility of the enhanced synergistic activation endowed by the pyrazole moiety, the cascade sulfa-Michael-aldol reaction of 2-mercaptobenzaldehyde (**1**) with the easily-available *N*-pyrazole crotonamide (**2a**) bearing a methyl group at the β-position was performed in DCM with bifunctional amine–thiourea catalysts[11,12] (Fig. 2), and the representative results are summarized in Table 1. Amine–thioureas **I** developed in this lab[9,13] were revealed to be highly efficient for this transformation, and the reaction went to completion at room temperature in less than 1 h (entries 1–4). However, the desired adduct **3a** was formed in unsatisfied diastereoselectivity with moderate to good enantioselectivity for the major diastereomer. Some other commonly used amine–thiourea catalysts were then evaluated to further improve the stereoselectivities of this process. To our delight, amine–thioureas **III–VI** derived from cinchona alkaloids were revealed as the best catalysts in terms

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‡ X.-Q. Dong and X. Fang contributed equally to this work.

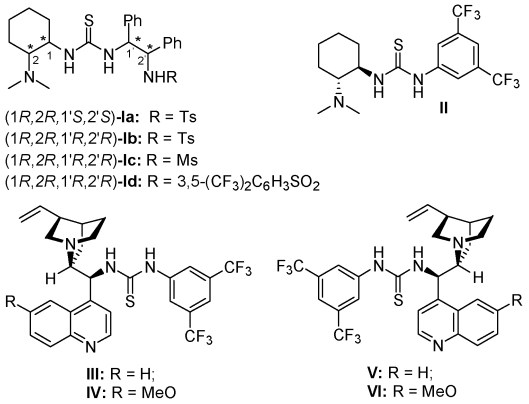
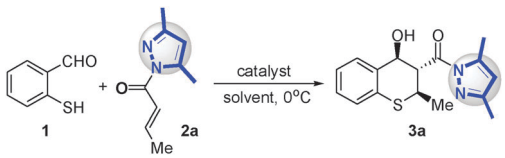


Fig. 2 Screened bifunctional amine–thiourea organocatalysts.

Table 1 Screening studies of cascade sulfa-Michael addition–aldol reaction of 2-mercaptobenzaldehyde **1** with *N*-pyrazole crotonamide **2a**[a]



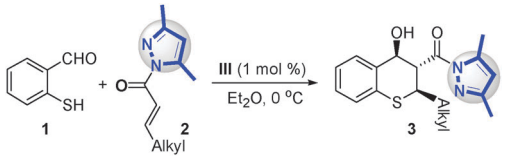
Entry	Catalyst	Solvent	Time/h	Yield[b] (%)	dr[c]	ee[c] (%)
1	**I–a** (10 mol%)	DCM	1	88	75 : 25	73
2	**I–b** (10 mol%)	DCM	1	85	74 : 26	95
3	**I–c** (10 mol%)	DCM	1	79	77 : 23	94
4	**I–d** (10 mol%)	DCM	1	90	89 : 11	97
5	**II** (10 mol%)	DCM	1	88	83 : 17	94
6	**III** (10 mol%)	DCM	1	90	96 : 4	98
7	**IV** (10 mol%)	DCM	1	89	88 : 12	−92
8	**V** (10 mol%)	DCM	1	86	92 : 8	−95
9	**VI** (10 mol%)	DCM	1	83	93 : 7	96
10	**III** (1 mol%)	DCM	4	89	94 : 6	97
11	**III** (0.5 mol%)	DCM	7	90	93 : 7	97
12	**III** (1 mol%)	Et_2O	4	90	98 : 2	98
13	**III** (1 mol%)	THF	4	90	96 : 4	97
14	**III** (1 mol%)	EtOAc	4	91	94 : 6	94
15	**III** (1 mol%)	PhMe	4	89	93 : 7	95
16	**V** (1 mol%)	Et_2O	4	90	95 : 5	−93

[a] All the reactions were carried out with 0.3 mmol of **1**, 0.33 mmol of **2a** in 1.0 mL of solvent. [b] Isolated yield. [c] Determined by HPLC analysis.

of yields and stereoselectivities (entries 6–9). Subsequently, catalyst **III** was chosen for further optimization of the reaction conditions. A comparable result was still achieved when catalyst loading was reduced to 1 mol% (entry 10). Further reducing the catalyst loading to 0.5 mol% showed that high yield and enantioselectivity remained albeit with a little longer reaction time (entry 11). A study of the reaction with 1 mol% catalyst **III** in various solvents identified that ether was the best solvent (entry 12). Of note is that cinchonine-derived thiourea **III** and cinchonidine-derived thiourea **V** as catalysts provided access to the opposite enantiomer of the cycloadduct with excellent diastereoselectivity and enantioselectivity (entry 16).

In the presence of 1 mol% of catalyst **III** in ether at 0 °C, the cascade sulfa-Michael–aldol reaction of 2-mercaptobenzaldehyde with various β-alkyl substituted α,β-unsaturated *N*-acyl pyrazoles was carried out to test the generality of the reaction. As shown in Table 2, substrates with a primary *n*-alkyl substituent such as methyl, ethyl, *n*-propyl, *n*-pentyl, or a phenethyl group

Table 2 Asymmetric cascade sulfa-Michael–aldol reaction of **1** with β-alkyl substituted α,β-unsaturated *N*-pyrazole-derived amide **2**[a]



Entry	Alkyl	4	Yield[b] (%)	dr[c]	ee[c] (%)
1	Me (**2a**)	**3a**	88	98 : 2	98
2	Et (**2b**)	**3b**	85	97 : 3	96
3	Pr (**2c**)	**3c**	72	97 : 3	97
4	*i*-Pr (**2d**)	**3d**	80	93 : 7	91
5	*n*-Pentyl (**2e**)	**3e**	88	96 : 4	97
6[d]	Cy (**2f**)	**3f**	65	96 : 4	93
7[d]	n-C_8H_{17} (**2g**)	**3g**	90	98 : 2	98
8	$PhCH_2CH_2$ (**2h**)	**3h**	70	94 : 6	98

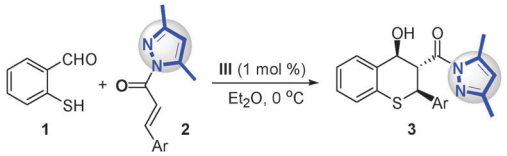
[a] All the reactions were carried out with 0.3 mmol of **1**, 0.33 mmol of **2** in 1.0 mL of solvent. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Carried out with 5 mol% catalyst at −10 °C.

at the β-position of the α,β-unsaturated *N*-acyl pyrazole all have afforded high diastereoselectivity and excellent enantioselectivity (entries 1–3 and 5). The decreased reactivity for α,β-unsaturated *N*-acylimide **2g** with longer carbon chain n-C_8H_{17} at the β-position could be improved through increasing the catalyst loading to 5 mol%, and the stereoselectivity is maintained at a similar level (entry 7). To further probe the steric effects of the substituent on this catalytic system, several substrates with branched and sterically bulky substituents at the β-position such as iso-propyl and cyclohexyl were employed, and a slight decrease in the enantioselectivity was observed, which was probably caused by the unfavored steric congestion (entries 4 and 6).

Encouraged by the excellent results for the challenging β-alkyl substituted α,β-unsaturated *N*-acylimide, we then investigated the cascade reaction of β-aryl substituted *N*-acyl pyrazole to further investigate the generality of this methodology. As shown in Table 3, α,β-unsaturated *N*-acylpyrazoles bearing electron-rich (entries 2–5), electron-neutral (entries 1 and 10), and electron-deficient groups (entries 6–9) on the aryl rings reacted with 2-mercapto-benzaldehyde **1** smoothly, affording the corresponding thiochromanes (**3i–3s**) in good yields (85–94%), excellent diastereoselectivities (95 : 5–99 : 1) and good enantioselectivities (95–99%) at 0 °C in ether within 4–7 h. The substitution pattern and electronic property of the phenyl ring have little effect on the enantioselectivity. It is noteworthy that comparable results were still achieved for the sterically hindered *ortho*-substituted *N*-acylimide **2j** and **2n** in terms of diastereo-/enantioselectivity and reactivity (entries 2 and 6). Additionally, the heteroaromatic substituted *N*-acylpyrazole **2s** was also a viable substrate as 2-naphthylaldehyde derived *N*-acylpyrazole **2r**, affording the corresponding product with 95 : 5 dr and 95% ee (entries 10–11).

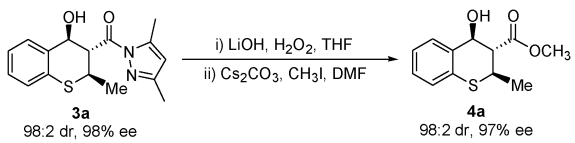
The optically active adducts containing three tertiary stereogenic centers can be readily transformed into a synthetically useful compound as exemplified in Scheme 1. The corresponding chiral β-hydroxyl carboxylic acid derivative **4a** can be easily obtained through cleavage of the pyrazole

Table 3 Asymmetric cascade sulfa-Michael–aldol reaction of **1** with β-aryl substituted α,β-unsaturated *N*-pyrazole-derived amide (**2**)[a]

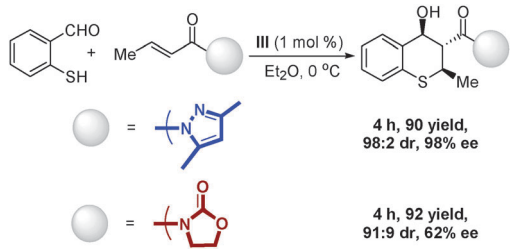


Entry	Ar	4	Yield[b] (%)	dr[c]	ee[c,d] (%)
1	Ph (**2i**)	**3i**	87	99 : 1	99
2	*o*-Me-Ph (**2j**)	**3j**	85	98 : 2	99
3	*m*-Me-Ph (**2k**)	**3k**	88	97 : 3	99
4	*p*-Me-Ph (**2l**)	**3l**	89	98 : 2	98
5	*p*-MeO-Ph (**2m**)	**3m**	86	97 : 3	97
6	*o*-Cl-Ph (**2n**)	**3n**	90	97 : 3	97
7	*m*-Cl-Ph (**2o**)	**3o**	92	95 : 5	98
8	*p*-Cl-Ph (**2p**)	**3p**	90	98 : 2	99
9	*p*-Br-Ph (**2q**)	**3q**	94	98 : 2	97
10	2-Naphthyl (**2r**)	**3r**	87	97 : 3	99
11	2-Furyl (**2s**)	**3s**	91	95 : 5	95

[a] All the reactions were carried out with 0.3 mmol of **1**, 0.33 mmol of **2** in 1.0 mL of solvent. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The absolute configuration of **3r** was unequivocally determined to be (2*S*,3*R*,4*S*) by X-ray crystallographic analysis (see ESI).



Scheme 1 Synthetic transformation of the sulfa-Michael–aldol adduct **3a**.



Scheme 2 Control experiments to evaluate the role of the amide moiety under the optimized reaction conditions (pyrazole *vs.* oxazolidineone).

moiety[14] and then esterification without loss of diastereo/enantiomeric excess.

In order to evaluate the role of the pyrazole motif played in this domino sulfa-Michael–aldol reaction, control experiments were carried out under the optimized reaction conditions (Scheme 2): for α,β-unsaturated *N*-acylimide bearing methyl at the β-position, replacing the oxazolidineone group with the pyrazole group led to a superior level of enantioselectivity and diastereoselectivity with the same sense of diastereoselectivity, which demonstrated that introducing the pyrazole moiety into the crotonamide plays a significant role in providing H-bond acceptor sites for better organization and chelation and hence delivering higher enantioselectivity compared with that of employing oxazolidineone as the corresponding amide moiety.

In summary, we have developed an efficient protocol for the direct construction of highly substituted and biologically active thiochromanes *via* an organocatalyzed asymmetric cascade sulfa-Michael–aldol reaction of 2-mercaptobenzaldehyde with various α,β-unsaturated *N*-acylimide bearing pyrazole moieties, which provided H-bond acceptor sites for better chelation and asymmetric induction, leading to excellent diastereoselectivity and enantioselectivity for both β-aryl and β-alkyl α,β-unsaturated *N*-acylimide.

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