One-pot approach to chiral chromenes *via* enantioselective organocatalytic domino oxa-Michael–aldol reaction†

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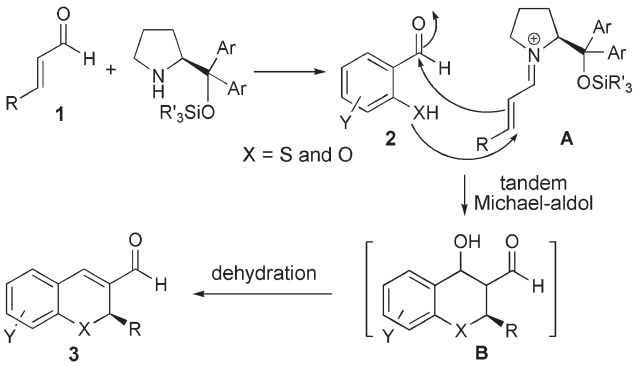
Received (in Bloomington, IN, USA) 9th August 2006, Accepted 16th October 2006
First published as an Advance Article on the web 1st November 2006
DOI: 10.1039/b611502k

A highly enantioselective (*S*)-diphenylpyrrolinol triethylsilyl ether promoted tandem oxa-Michael–aldol reaction of α,β-unsaturated aldehydes with salicylaldehydes has been developed; the method affords one-pot access to chiral and synthetically useful chromenes in high yields and high enantioselectivities from readily available compounds.

Functionalized chiral chromene skeleton is found in a myriad of medicinally important compounds that have a broad and interesting range of biological activities.[1,2] Accordingly, a number of synthetic strategies have been reported for the construction of this "privileged" structural motif.[3] Although asymmetric methods would furnish enantiomerically enriched chromenes, their development has proven to be a synthetic challenging task. To date, approaches to chiral chromenes involving ring-closing metathesis[2e,4] and Pt-catalyzed cyclization[5] of chiral precursors and enzyme-catalyzed kinetic resolution[6] have been described. An enantioselective procedure, based on a chiral metal–ligand complex, has been recently reported by Malinakova and co-workers[7] for generation of this chiral scaffold. However, it is noted that a stoichiometric amount of the complex is used. In this communication, we wish to report a new one-pot, enantioselective organocatalytic domino oxa-Michael–aldol reaction for the facile preparation of chiral chromenes. The process takes place in high yields (up to 98%) and with good to excellent levels of enantioselectivities (up to >99% ee). Importantly, this approach allows for the construction of complex benzopyran structures starting with simple α,β-unsaturated aldehydes and salicylaldehydes.

By taking advantage of the capability of chiral pyrrolidine derivatives to participate in the reversible formation of enamine and iminium intermediates, Barbas, Yamamoto, List, MacMillan, Jørgenson, and Enders have independently developed novel types of organocatalyzed cascade reactions.[8,9] Michael addition initiated cascade Michael–aldol processes serve as powerful methods for the generation of complex structures. We envisioned that an "S" or "O" could serve as a Michael donor for initiating the process (Scheme 1). Recently, we have demonstrated that 2-mercaptobenzaldehydes can participate in the tandem reactions with attaining high enantioselectivity (85–95% ee).[10–12] However, the development of "O" invoked Michael–aldol process has created a formidable challenge since the oxygen in phenol is a much weaker



Scheme 1 Domino organocatalyzed enantioselective Michael–aldol reactions.

nucleophile than that of the sulfur of thiophenol.[10,13] Generally, a base is used to activate the Michael donor phenol group **2** and these methods are non-asymmetric.[10] The strategy we present here is the utilization of a chiral organocatalyst as a promoter for activation of the Michael acceptor **1** in a highly enantioselective controlled manner (Scheme 1).

A model reaction between *trans*-cinnamaldehyde **1a** and salicylaldehyde **2a** in toluene at r.t. under the same reaction conditions used for the tandem thio-Michael–aldol reaction[11] in the presence of organocatalyst **I** was evaluated for the oxa-Michael–aldol process (Fig. 1 and Table 1). It was found that, surprisingly, no reaction occurred even using 30 mol% catalyst (Table 1, entry 1). The result prompted us to survey (*S*)-diphenylpyrrolinol TMS ether **II** for the process (Fig. 1).[14–16] To our delight, the reaction proceeded with achieving a good yield (70%), but a moderate ee (52%) (entry 2). After extensive optimization reaction conditions including screening solvents[17] and reaction temperature, we found that using $Cl(CH_2)_2Cl$ as a solvent provided the highest enantioselectivity (80% ee, entry 3). Lowering the reaction temperature to 0 °C resulted in an improved ee (89%) but the time required for completion was significantly lengthened (60 h) and the yield was decreased as well (entry 4). Switching the TMS silyl ether in catalyst **II** to the TES in **III** (entry 5) and TBS in **IV** (entry 6) showed that **III** was a superior catalyst (87% yield and 88% ee, entry 5).

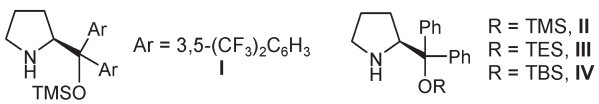


Fig. 1 Screened organocatalysts.

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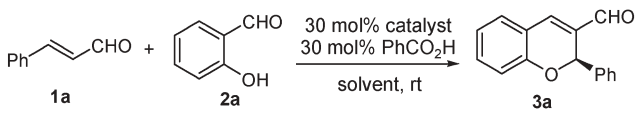
† Electronic supplementary information (ESI) available: Experimental and NMR data. See DOI: 10.1039/b611502k

Table 1 Organocatalytic asymmetric domino oxa-Michael–aldol reaction of *trans*-cinnamaldehyde (**1a**) with salicylaldehyde (**2a**)[a]

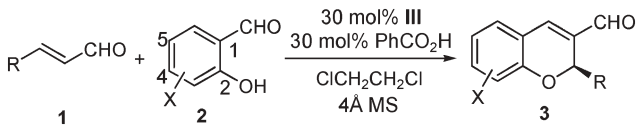


1a 2a 3a

Entry	Cat.	Solvent	*t*/h	Yield[b] (%)	ee (%)[c]
1	**I**	Toluene	36	<5	ND[d]
2	**II**	Toluene	48	70	52
3	**II**	$Cl(CH_2)_2Cl$	22	91	80
4[e]	**II**	$Cl(CH_2)_2Cl$	60	51	89
5[e]	**III**	$Cl(CH_2)_2Cl$	60	87	88
6[e]	**IV**	$Cl(CH_2)_2Cl$	96	52	80

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.1 mmol) and **2a** (1.0 mmol) in the presence of an organocatalyst (0.03 mmol), benzoic acid (0.03 mmol), 4 Å MS (50 mg), and solvent (0.5 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis (Chiralpak AS-H). [d] Not determined. [e] Performed at 0 °C.

Table 2 Catalyst **III** promoted domino oxa-Michael–aldol reactions of α,β-unsaturated aldehydes (**1**) with salicylaldehydes (**2**)[a]



1 2 3

Entry	R	X	*T*/°C	*t*/h	Yield[b] (%)	ee[c] (%)
1	Ph	H	0	60	87	88
2	$4\text{-}NO_2C_6H_4$	H	0	24	96	95
3	$4\text{-}NO_2C_6H_4$	5-Me	0	18	98	96
4	$4\text{-}NO_2C_6H_4$	5-Cl	0	18	96	91
5	$4\text{-}NO_2C_6H_4$	4-MeO	r.t.	120	64	86
6	$4\text{-}NO_2C_6H_4$	3-MeO	0	36	98	90
7	$4\text{-}NO_2C_6H_4$	5-MeO	−15	24	95	94
8	$2\text{-}NO_2C_6H_4$	5-Cl	−15	144	82	>99
9	Ph	5-MeO	0	48	97	87
10	$4\text{-}MeOC_6H_4$	5-Cl	4	72	53	75
11	Me	5-Cl	0	36	67	82
12	Me	5-MeO	0	48	84	85

[a] *Reaction conditions*: unless specified, see footnote *a* in Table 1. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H, or Chiralcel OD-H).

Having established optimal conditions for reaction of *trans*-cinnamaldehyde **1a** and salicylaldehyde **2a** to form the chromene **3a** in $ClCH_2CH_2Cl$ promoted by catalyst **III**, we next probed the scope of the domino oxa-Michael–aldol process by using a variety of α,β-unsaturated aldehydes **1** and salicylaldehydes **2**. As the data in Table 2 show, the reactions proceeded in respectively high yields (53–98%) and with good to excellent levels of enantioselectivities (75–99% ee) (Table 2). The process appeared to have a broad scope, but efficiencies and ees varied with the electronic and steric nature of the α,β-unsaturated aldehydes **1** and salicylaldehydes **2**. α,β-Unsaturated aldehydes **1** bearing electron-withdrawing groups, such as nitro group, generally afforded products in higher yields (82–98%) and higher ee values (86–99%, entries 2–8) than those not possessing electron withdrawing groups. Relatively lower ees were observed for reactions of α,β-unsaturated aromatic aldehydes **1** that bear neutral (entries 1 and 9) or electron-donating (entry 10) substituents. Also, the results showed that steric hindrance retarded the reactions but enhanced enantioselectivities (entry 8). The **III**-catalyzed processes also took place with less reactive alkyl-substituted α,β-unsaturated aldehydes (entries 11 and 12), albeit with lower yields and enantioselectivities. Significant structural variation in the salicylaldehydes **2** was tolerated in the process. Aromatic rings, bearing electron neutral (entries 1–2), withdrawing (entries 4, 8, 10 and 11) and donating (entries 3, 5–7, 9 and 12) groups could undergo the **III**-promoted cascade process efficiently.

In summary, we have uncovered a one-pot organocatalyzed domino oxa-Michael–aldol reaction that transforms readily available α,β-unsaturated aldehydes and 2-salicylaldehydes to synthetically and biologically useful chiral chromenes in high enantiomeric purities. Investigations of the full scope of the cascade reaction, and its application to the synthesis of biologically interesting compounds are underway and the results will be reported in due course.

Financial support for this work provided by the Department of Chemistry and the Research Allocation Committee, the University of New Mexico, the ACS-PRF and NIH-INBRE (P20 RR016480) is gratefully acknowledged.

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17 Xylenes: 96% yield, 40% ee; anisole: 56% yield, 66% ee; CH_2Cl_2: 81% yield, 76% ee; $CHCl_3$: 68% yield, 67% ee; CCl_4: 65% yield, 47% ee; Et_2O: 85% yield, 43% ee; dioxane: <5% yield; DMSO: 66% yield, 60% ee.