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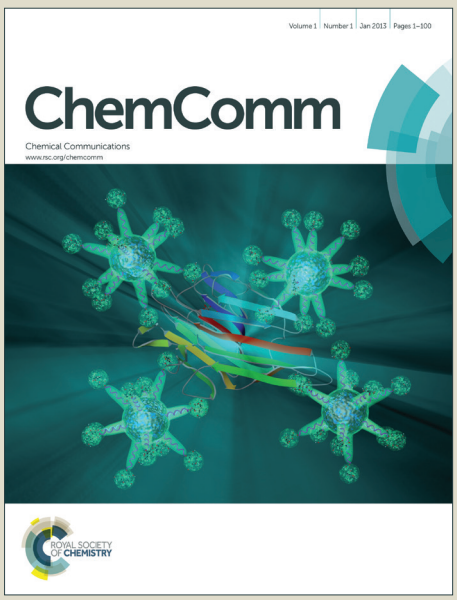

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ARTICLE TYPE

Enantioselective cascade reaction between α,β-unsaturated aldehydes and malonic half-thioesters: rapid access to chiral δ-lactones

Qiao Ren,[a,b] Shaofa Sun,*[a] Jiayao Huang,[b] Wenjun Li,[b] Minghu Wu,[a] Haibing Guo[a] and Jian Wang*[a,b]

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We disclose a novel efficient enantioselective organocatalytic cascade reaction for the preparation of δ-lactones in good to excellent yields (69-93%) and with high to excellent enantioselectivities (88-96% *ee*).

The assembly of *O*-heterocycles is an important field of research due to their prevalence in natural products and drugs.[1] Of the *O*-heterocycles, δ-lactones are well-known six-membered oxygen-containing heterocycles that form the structural scaffold of many biologically active molecules,[2] hence, they are broadly used in medicinal chemistry as important structural elements. Notably, a large number of δ-lactones involved biologically active important molecules exist in a single enantiomer.[2,3] As exemplified in Figure 1, Lovastatin[4] **a** marketed by Merck under the trade name Mevacor, is a member of the drug class of statins, used in the treatment of dyslipidemia and the prevention of cardiovascular disease. Artemisitene[5] **b**, isolated from *Artemisia annua* L., has been shown to possess antimalarial activity. Crassin acetate[6] **c**, a lactonic cembrane diterpene, has been shown to be the principal antineoplastic agent present in the marine invertebrates. Leiodermatolide[7] **d** is a structurally unique macrolide isolated from the deep-water marine sponge *Leiodermatium* sp. which exhibits potent antiproliferative activity against a range of human cancer cell lines and drastic effects on spindle formation in mitotic cells.

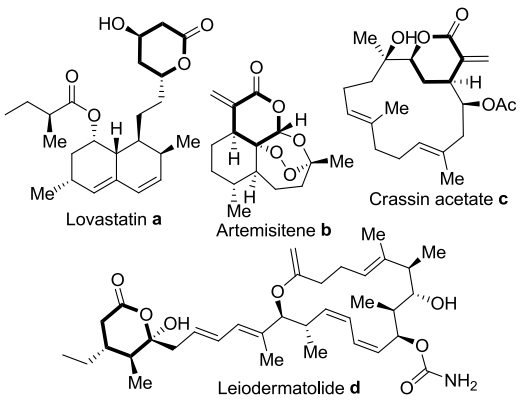
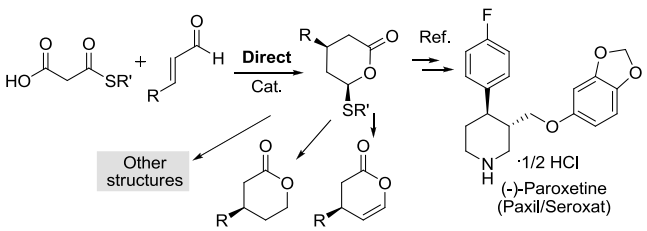


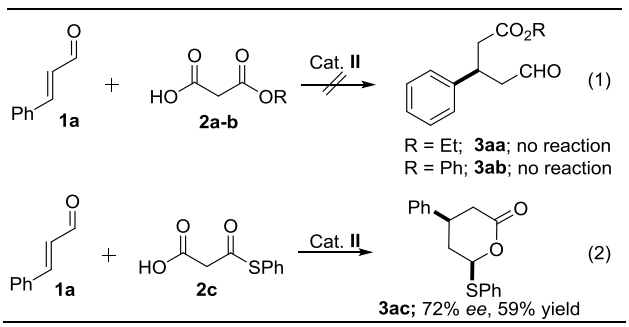
Figure 1: Examples of natural products or drugs contacting δ-lactone moiety.

Notably, chiral pharmaceuticals are figuring largely in drug market. Most of beneficial drugs are sold as a single enantiomeric form because of the higher efficiency than its mirror image enantiomer and displaying better fit to its receptor. In addition, it may even be encountered with harmful results with the other enantiomer.[8] Given the fact that within a chiral surrounding two enantiomers often show distinct biological activity, the development of effective protocols to access optical pure δ-lactones would be extremely desirable to further study the correlation between the chirality of these compounds and their propensities for biological activities to seek more potent and/or appropriate pharmaceutical candidates. In our continuing effort towards the development of new approaches for the stereoselective construction of enantiopure synthetically useful building blocks,[9] we thought about expanding the scope of organocatalytic decarboxylative reactions[10,11] to α,β-unsaturated aldehydes[12]. Although many methods have been reported on chiral δ-lactone synthesis, most of them were prepared for the assembly of α,β- or γ,δ-unsaturated δ-lactones.[13,14] Herein, we disclose a direct and efficient enantioselective cascade strategy for the saturated functional δ-lactone synthesis (Scheme 1).



Scheme 1: Efficient synthesis of chiral δ-lactones and related transformations.

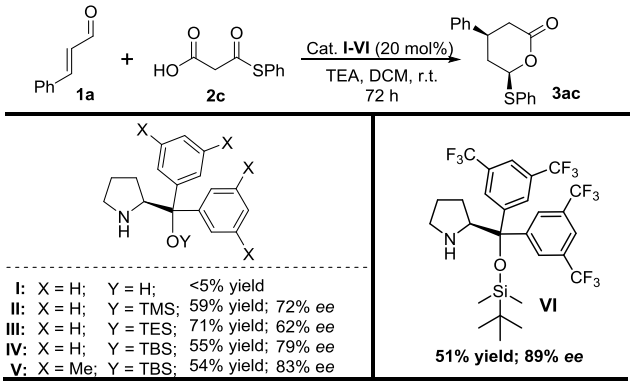
Scheme 2: Initial Experiments.



Reaction Conditions: **1a** (0.20 mmol), **2** (0.24 mmol), TEA (0.20 mmol), Cat. **II** (0.20 mmol), DCM (1.0 mL), 72 h, room temperature.

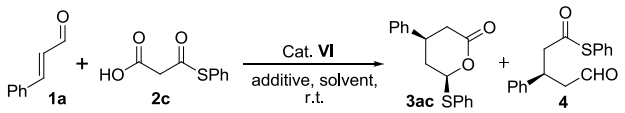
During our initial studies on the feasibility of amine-catalyzed intermolecular reactions of malonic acid mono-protected esters (**2a**–**b**) with cinnamaldehyde (**1a**), no decarboxylative adducts were observed (Scheme 2). In the context of exploring a plausible catalytic process, we turned our attention to investigate malonic acid analogous. As shown in Scheme 2, the malonic half-thioester (**2c)** was found to be a suitable partner to allow the reaction to promote smoothly in the presence of prolinol catalyst **II** (Table 1). Interesting, an unexpected δ-lactone (**3ac**) was identified as a major product (59% yield, 72% *ee*). Screening of catalysts revealed that the size of silyl ether moiety in catalysts (Cat. **I-VI**) is critical for the stereocontrol. As outlined in Table 1, the most bulky catalyst *tert*-butyltrimethylsilane ether **VI** (TBDMS) gave the best result (Table 1, 89% *ee*, 51% yield). Subsequent solvent survey (Table 2, entries 1 and 4–6) indicated that DCM is an ideal medium for this asymmetric transformation (entry 7, 89% *ee*). Other parameters (*e.g.* bases) gave no improvement on *ee* value (Table 2, entries 2–3). It is noteworthy that acyclic 3-phenyl 1-aldehyde 5-thioester **4** was formed as a major product when Na_2CO_3 instead TEA. Gratify, the dropwise addition pattern of TEA gave a better result (92% *ee*, 82% yield). Controlled experiment indicated that one-pot addition of TEA could cause a rapid decomposition of malonic half-thioester **2c**.

Table 1: Screened catalysts.



Reaction condition: **1a** (0.20 mmol), **2a** (0.24 mmol), TEA (1.0 equiv.), Cat. **I-VI** (20 mol%), DCM (1.0 mL), 72 h, room temperature.

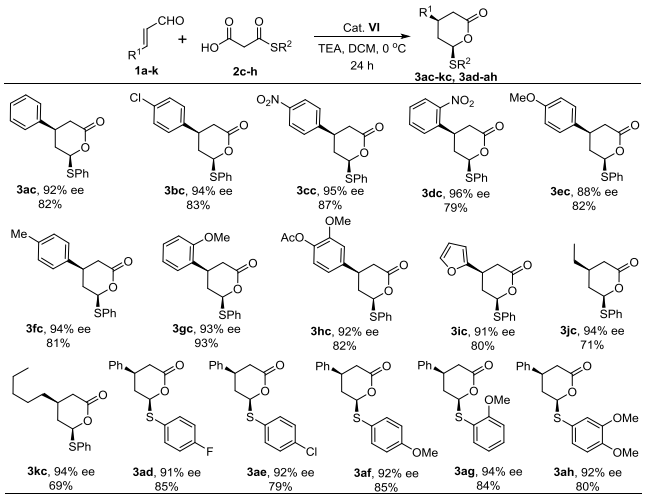
Table 2: Optimization of other reaction parameters.[a]



Entry	Additive	Solvent	**3ac** (%)[b]	**3ac** *ee* (%)[c]
1	TEA	DCM	51	89
2	Na_2CO_3	DCM	22(**4**)	18
3	TBD[g]	DCM	37	78
4	TEA	Toluene	53	81
5	TEA	THF	47	84
6	TEA	IPA[f]	47	89
7[d]	TEA	DCM	57	89
8[d,e]	TEA	DCM	82	92

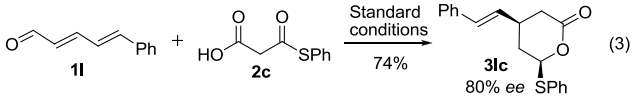
[a] Reactions were performed with **1a** (0.20 mmol), **2c** (0.24 mmol), additive (0.20 mmol) in the solvent (1.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] **2c** (0.50 mmol), TEA (0.50 mmol). [e] TEA dissolved in 0.50 mL of DCM was added dropwise in 10 min, 0 °C. [f] Isopropanol. [g] 1,5,7-Triazabicyclo[4.4.0]dec-5-ene.

Table 3: Substrate scope of α,β-unsaturated aldehydes.[a-d]



[a] Reaction conditions: **1a**-**k** (0.20 mmol), **2c**-**h** (0.50 mmol), TEA (0.50 mmol) and catalyst **VI** (0.04 mmol), DCM (1.0 mL), 0 °C for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] all dr > 20:1.

After having optimized the conditions for the cascade reaction, the scope of the methodology was evaluated. Initially, various α,β-unsaturated aldehydes **1** with different substitution patterns and electronic properties were examined (Table 3). The substitution patterns of malonic half-thioesters had limited impact on the yields or enantioselectivities, thereby providing the only regioisomer with *ee* values ranging from 91 to 94% (Table 3, **3ac**–**ah**, all dr > 20:1). Pleasingly, α,β-unsaturated aldehydes **1a**–**h** bearing different electron-withdrawing substituents on the aromic ring were easily reacted under the established reaction conditions (**3ac**–**hc**). In most of the cases, good yields and high steroselectivities were obtained.[17] Additionally, α,β-unsaturated aldehydes **1i**–**k** bearing heterocyclic rings and alkyl groups could be utilized as well in good yields with rigorous steroselectivities (**3ic**–**kc**).[15] Additionaly, α,β,γ,δ-unsaturated aldehyde **1l** could react with **2c** to afford 3-alkenyl δ-lactone **3lc** in 74% yield and with 80% *ee* (eqn (3)).

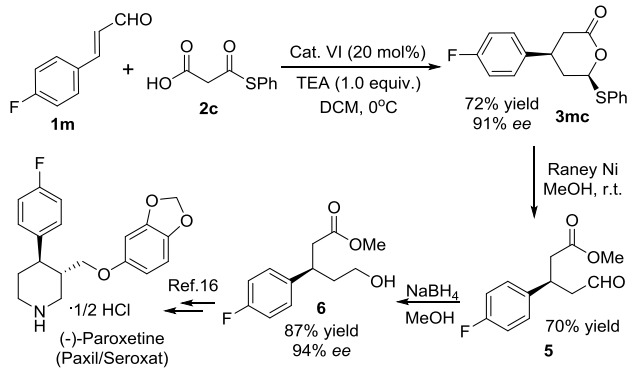


Further application study was embarked on examining the applicability of our method to the concise synthesis of (-)-Paroxetine, marketed as Paxil/Seroxat (Scheme 3). The reaction of **1m** with **2c** catalyzed by **VI** and TEA gave the corresponding **3mc** in 72% yield and 91% *ee* (Scheme 3). Next, Ni-catalyzed ring opening reaction gave the corresponding 3-substituted 1,5-dicarbonyl **17**, and a subsequent reduction of **17** afforded the key intermediate **18**. According to reported procedure,[16] the intermediate **18** can be converted to target (-)-Paroxetine, an antidepressant drug.

In summary, we have established a new method for the enantioselective cascade synthesis of δ-lactone in the presence of chiral prolinol or cinchona alkaloid amine organocatalysts. Our methodology provided a straightforward way to generate valuable chiral δ-lactone scaffold, which has potentially biological

significance in the field of medicinal chemistry. The ready accessibility of the starting materials makes the current methodology particularly attractive in organic synthesis. Studies towards expanding the synthetic utility of this strategy are currently underway.

Scheme 3: Formal total synthesis of (-)-Paroxetine (Paxil/Seroxat).



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Notes and references

[a]*Hubei Collaborative Innovation Centre for Non-power Nuclear Technology, College of Chemistry and Biological Sciences, Hubei University of Science and Technology, Hubei Province 437100, People's Republic China*

[b]*Department of Chemistry,National University of Singapore, Block S15, Level 5, 3 Science Drive 3,* Singapore 117543. *Fax: 65-6779-1691; E-mail: chmwangj@nus.edu.sg*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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