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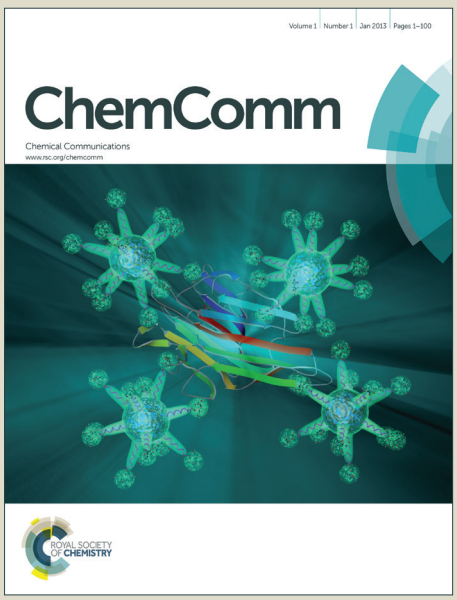

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Organocatalytic Enantio- and Diastereoselective Synthesis of Highly Substituted δ-Lactones *via* Michael-Cyclization Cascade

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An organocatalyzed Michael-cyclization cascade approach of readily available α,β-unsaturated aldehydes and pyrazoleamides has been developed to get highly substituted δ-lactones in excellent enantioselectivities (up to 97%) and diastereoselectivities. The δ-lactones so obtained could easily be transformed to benzazepine derivatives with excellent enantio- and diastereoselectivities. Furthermore, pyrazole moiety from the δ-lactones can be simply cleaved without disturbing the stereoselectivity.

One-pot synthesis of complex heterocyclic organic motifs containing multi stereo centres in highly enantio- and diastereoselective fashion has been the key interest of current research in view of operationally simplicity, atom efficiency and overall cost reduction of desired compounds.[1] Synthesis of enantiomerically enriched highly functionalized six membered *O*-heterocyclic δ-lactones has received much attention because of their wide range of biological activities.[2] The importance of enantiomerically pure δ-lactones are evident from the vital structure scaffolds of many natural products and pharmaceuticals,[3] such as Vernolepin, Prelactone B, Teucriumlactone, Lovastatin, Leiodermatolide (Figure 1) which has been shown to possess anti-malarial, anti-inflammatory, anti-viral, anti-neoplastic agent and anti-proliferative activity against human cancer cell line.[4]

In the past decade, methods involved towards the development of enantio- and diastereoselective synthesis of these targets include an asymmetric Diels-Alder cyclization,[5] enzymatic transformations,[6] dynamic kinetic resolutions of carbonyl racemates (DKR),[7] organocatalyzed Michael addition/lactonization cascade of α,β-unsaturated carbonyl compounds with ketones,[8] esters,[9] carboxylic acids[10] and through organocatalyzed intramolecular halolactonization of olefinic acids.[11] However, most of these approaches either proceed through multistep production or require more than one external reagent to obtain the desired δ-lactones.[12] Till date, to the best of our knowledge there is no straightforward synthetic method available for the synthesis of poly functionalized enantio- and diastereoselective δ-lactones. Furthermore, amide pronucleophiles has not been much investigated in such type of δ-lactones synthesis. Recently, pyrazoleamides have been used as an exceptional nucleophile in organocatalyzed asymmetric reactions.[13] It is worth noting that pyrazoleamides can directly be synthesized from carboxylic acid.[13a] Additionally, the pyrazole moiety of former nucleophile has been considered as a directing group for enhancing the enantio- and diastereoselectivity with advantage of good leaving group for further transformations. Herein, we demonstrate an organocatalytic one-pot highly enantio/diastereoselective Michael-cyclization cascade approach from readily available α,β-unsaturated aldehydes and pyrazoleamides.

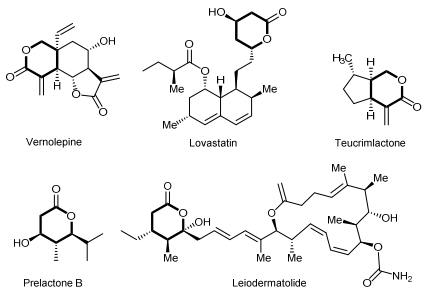
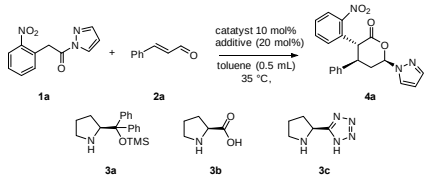


Figure 1. δ-lactones containing some important natural products.

At the outset, pyrazoleamide (**1a**) and cinnamaldehyde (**2a**) were chosen as model substrates for Michael-cyclization cascade approach in toluene at 35 °C reaction temperature. In the presence of proline-derived organocatalyst **3a** (10 mol%), interestingly δ-lactone **4a** was isolated in 78% yield with a unique structural feature. It shows that during this cascade, migration of pyrazole moiety from carbonyl carbon of pyrazoleamide to carbonyl carbon of α,β-unsaturated aldehydes takes place. This indicates, that this cascade involves a C-C bond breaking and a new C-N bond forming steps. Stereochemical outcome of δ-lactone **4a** acquires moderate ee (60%) with excellent

distereoselectivity (Table 1, entry 1). On further screening of organocatalysts, we found that *L*-proline (**3b**) as an organocatalyst furnished **4a** in poor yield and enantioselectivity (entry 2) while organocatalyst (**3c**) did not work (entry 3). Results summarized in table 1 clearly indicates that, an addition of acidic and basic additives (20 mol%) in this cascade affected the outcome in terms of yield and ee of δ-lactone **4a**. Among all tested additives, 4-nitrobenzoic acid (4-NBA) was found to be choice for further study (entry 7).

Table 1. Reaction optimization[a].

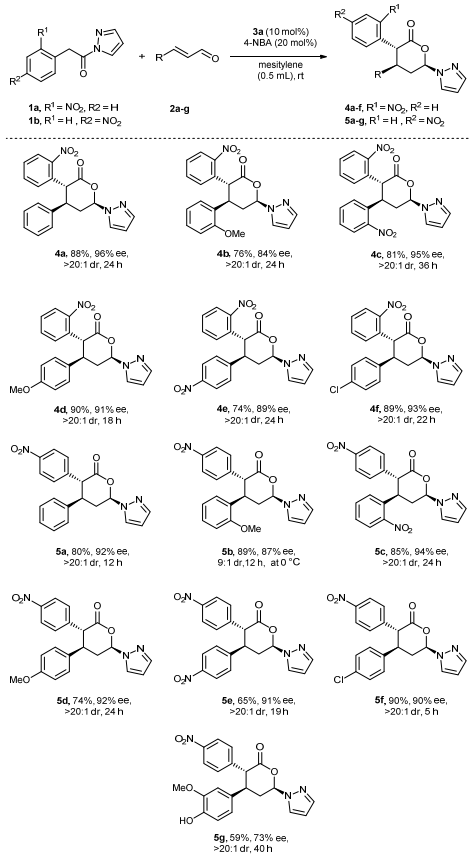


Entry	Catalyst	Additive	Yield[b] (%)	ee[c] (%)
1	3a	----	78	60
2	3b	---	22	8
3	3c	---	nd	nd
4	3a	NaOAc	80	56
5	3a	Quinine	79	85
6	3a	Benzoic acid	85	82
7	3a	4-Nitrobenzoic acid	89	85

[a]All reactions were carried out using 0.2 mmol of **1a** and 0.3 mmol of **2a** using toluene as solvent at 35 °C up to 12 h. [b]Isolated yield after column choromatography as single diastereomer.[c]Determined by HPLC using Diacel chiralpak IC column. Nd = not detected

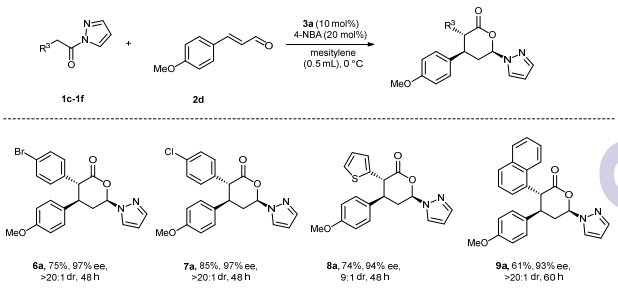
Solvent and temperature studies under standard reaction condition in the presence of catalyst **3a** and 4-NBA as an additive (see SI table S1) revealed mesitylene to be the best solvent to afford the Michael-cyclization cascade product in excellent yield and enantioselectivity at room temperature (25 °C).

Having established the optimal reaction conditions, we then evaluated the scope of various α,β-unsaturated aldehydes having *ortho*-, *para*-substituted phenyl ring (**2a-f**) with pyrazoleamide (**1a** and **1b**) for Michael-cyclization cascade approach (Scheme 1). The results revealed that both *ortho*- and *para*-substituted α,β-unsaturated aldehydes smoothly underwent this cascade transformation and corresponding δ-lactones (**4a-f**) were isolated in good to excellent yields (76-90%) with excellent enantioselectivities (89-96%). It is worth noting that in case of pyrazoleamide (**1b**) the Michael-cyclization cascade furnished in shorter reaction time and resulted δ-lactones (**5a-f**) obtained in good to excellent yields (65-90%) with excellent ee (87-94%). In case of more bulky substrate (*E*)-3-(4-hydroxy-3-methoxyphenyl) acryl aldehyde (**2g**), dichloromethane was used as a solvent instead of mesitylene to overcome the solubility problem associated with this substrate. δ-Lactone (**5g**) obtained in moderate yield (59%) and ee (73%) after 40 h. We also tested aliphatic α,β-unsaturated aldehydes such as crotonaldehye, *trans*-2-pentenal under the optimized reaction conditions. However, these substrates afforded a mixture of unidentified products.



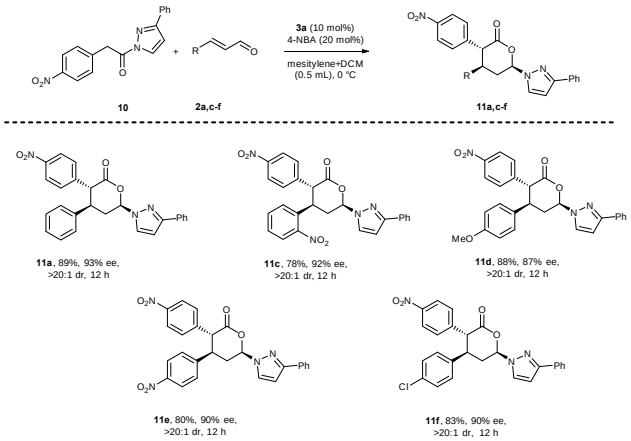
Scheme 1. Scope of various α,β-unsaturated aldehydes in Michael-cyclization cascade.

Next, Michael-cyclization cascade was further explored to a variety of pyrazoleamides (**1c-1f**) under the optimized reaction conditions with 4-methoxycinnamaldehye (**2d**) (Scheme 2). The reactivity of pyrazoleamide was highly affected by electronic properties of the phenyl ring. *p*-Bromo and *p*-chloro substituted pyrazoleamide (**1c** and **1d** respectively) furnished δ-lactones (**6a** and **7a**) in 48 h with 75% and 85% yield and excellent ee (97%) and diastereoselectivity (>20:1) respectively. Heteroaromatic pyrazoleamide (**1e**) produced the desired δ-lactone (**8a**) in good yield (74%) with diastereoselectivity (9:1) and excellent enantioselectivity (94%) of major diastereomer. Bulky pyrazoleamide (**1f**) took 60 h to give δ-lactone (**9a**) in moderate yield (61%) with excellent enantioselectivity (93%).



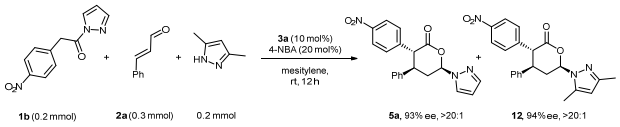
Scheme 2. Scope of various pyrazoleamide in Michael-cyclization cascade.

Michael-cyclization cascade protocol was further accomplished by the variation in pyrazole moiety of pyrazoleamide. 3-Phenylpyrazole containing pyrazoleamide (**10**) was tested with variety of α,β-unsaturated aldehydes (**2a,c-f**) under the optimized reaction conditions except that the reactions were carried out at 0 °C to achieve high enantioselectivity and dichloromethane as a co-solvent to homogenize the reaction mixture (Scheme 3). To our delight Michael-cyclization cascade protocol smoothly furnished the δ-lactones (**11a,c-f**) with excellent enantio- and diastereoselctivities.



Scheme 3. Pyrazoleamide 10 as a nucleophile in Michael-cyclization cascade.

To understand the reaction mechanism and rearrangement of pyrazole moiety, a cross over experiment was carried out under the standard reaction conditions by addition of 3,5-dimethylpyrazole (0.2 mmol) as an external nucleophile (Scheme 4), ^{1}H NMR of crude reaction mixture shows almost equal amount formation of products **5a** and **12** with high diastereoselectivity (see SI). Upon isolation both products shows excellent ee 93% and 94% respectively, suggesting in initial step pyrazole act as leaving group and as a nucleophile in consequent step. Based on cross-over experiment and obtained result, a plausible reaction pathway is depicted in figure 2. We assume



Scheme 4. Cross over experiment.

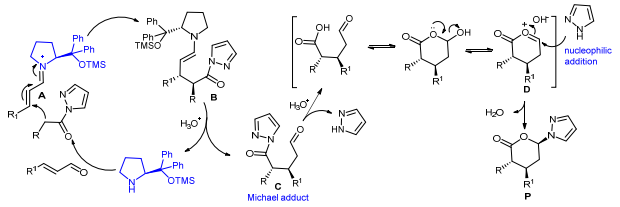


Figure 2. Plausible reaction pathway.

that the described organocatalytic Michael-cyclization cascade approach initiated by the formation of iminium ion **A**. Subsequent 1,4-conjugated addition of pyrazoleamide gives rise to intermediate **B**, which after hydrolysis gives Michael adduct **C** and followed by lactonization intermediate **D** generated. **D** then undergoes nucleophilc addition to pyrazole yields the desired δ-lactone **P** (Figure 2).

The configuration of the three generated stereocenters in δ-lactones was confirmed by single crystal analysis. A single crystal of product (**7a**) was obtained by slow evaporation of *n*-hexane/CHCl$_3$ solution of lactone (**7a**), and the configuration of all three stereocenters were unambiguously assigned "***R***" by X-ray crystal structure (CCDC 1045015) (Figure 3). All other δ-lactones within this series were assigned by analogy.

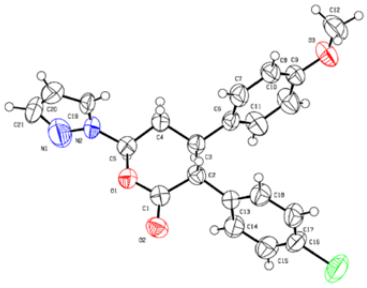
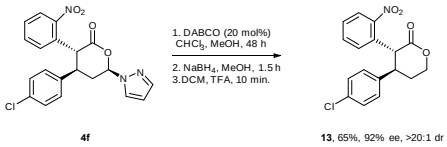
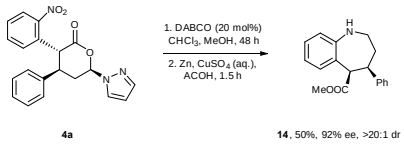


Figure 3: X-ray crystal structure (ORTAP) of (**7a**) with 50% ellipsoidal probability

Further, the synthetic utilities of these δ-lactones were investigated. δ-Lactone (**4f**) can be easily converted into δ-lactone (**13**) by detachment of pyrazole in excellent enanatioselectivity (92%) (Scheme 5). Furthermore δ-lactone (**4a**) is transformed to benzazepine derivative (**14**) in one-pot sequential process, in overall 50% yield with excellent enantioselectivity (92%) (Scheme 6). These benzazepine derivatives could serve as a key intermediate in the synthesis of 7-membered *aza*-heterocyclic aromatic chiral natural products, and several pharmaceutically active compounds.[14]



Scheme 5. Cleavage of pyrazole from δ-lactones (4f).



Scheme 6. Synthesis of benzazepine (**14**) from δ-lactones (**4a**).

In conclusion, we have developed a highly efficient enantio- and diastereoselective one-pot Michael-cyclization cascade approach for synthesis of a wide range of δ-lactones from readily available starting materials. The desired δ-lactones were obtained with high level of enantioselectivities (up to 97%) and diastereselectivity (up to >20:1) and excellent isolated yields (up to 92%). Finally, the cleavage of pyrazole moiety and enantioselective synthesis of benzazepine derivatives further increases the utility of the method. Newer cascade

approaches for the greener and economical production of highly functionalized molecules is under active investigation in our laboratory.

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Notes and references

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‡ Both the authors contributed equally to this work.
† Electronic Supplementary Information (ESI) available: The Copies of NMR spectra and HPLC chromatograms of all new compounds and crystal data of **7a**. CCDC 1045015 contains supplementary crystallographic data for the structure **7a**.

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