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Direct Organocatalytic Multicomponent Synthesis of Enantiopure γ-Butyrolactones via Tandem Knoevenagel-Michael-Lactonization Sequence

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Abstract. An expedient and straightforward protocol is developed for the synthesis of highly enantiopure synthesis of γ-butyrolactones. For the first time, one pot enantioselective organocatalytic multicomponent reaction (OMCR) is explored to construct functionalized butyrolactones without the use of pre-functionalized substrates and expensive transition metals. The protocol is proved to be reproducible on a gram scale. Density functional theory (DFT) calculations strongly support the mechanism and were in close agreement with the observed high stereoselectivity.

Keywords: Multocomponent reactions • Organocatalysis • γ-Butylrolactones • Enantioselectivity • Hetero-Diels-Alder reaction

Optically active γ-butyrolactone is one of the most abundant structural motifs in a wide array of biologically active natural products.[1] In fact, the γ-butyrolactone core constitutes about 10% of naturally occurring compounds[2] and many of these possess a broad range of biological activities and are known potent anticancer, antibacterial and antifungal agents.[3] In this regard, several multistep catalytic approaches have been explored for the racemic synthesis of γ-butyrolactones.[4] Considering the inevitable importance of γ-lactone scaffold, conspicuous efforts have been devoted towards the enantioselective synthesis of a γ-butyrolactone core with the catalytic approach.[5] Among these many enantioselective methods, most noteworthy are asymmetric transfer hydrogenation (Fig 1a),[5a-5c] gold catalyzed lactonization by Lipshutz (see Fig 1b)[5d] and chromium catalyzed γ-butyrolactone synthesis by Yun.[5e] However, some of these methodologies rely on the use of heavy and expensive transitional metal catalysts (Ir, Ru, Au, Cr, etc), very expensive ligands and commercially unavailable pre-functionalized starting materials. Notably, only countable organocatalyzed protocols such as asymmetric cross-benzoin/Michael/acetalization by Han,[5f] cross annulation by Saigo[5g] and Fiksdahl[5h] are limited only to highly reactive fluorinated ketones as substrates (See Fig 1c). Moreover, it is important to note that in other protocols only aromatic hydroxyketones are proved to be efficient precursors for the enantioselective synthesis of γ-butyrolactones and related compounds such as five membered oxygen heterocycles.[6] However, these multistep methods are limited to aromatic hydroxyketones and aromatic Michael acceptors. While the aliphatic hydroxyketones and aliphatic Michael acceptors did not react under the reaction conditions[6a] or they were not explored possibly due to the similar reasons.[6b] However, organocatalyzed enantiopure synthesis of γ-butyrolactones that involves easily and commercially available starting materials, and less reactive simple aliphatic as well as aromatic hydroxyketones in one step is much more challenging and demanding to pursue. Some of these synthetic limitations strongly encouraged us to explore the synthesis of enantiopure lactones by more convenient and practical approach. The key challenges are to avoid pre-functionalized starting materials and expensive transition metal catalysts. One-pot organocatalytic multicomponent reactions can prove to be one of the very important strategies to access the enantiopure γ-butyrolactones in a cost effective and efficient manner.

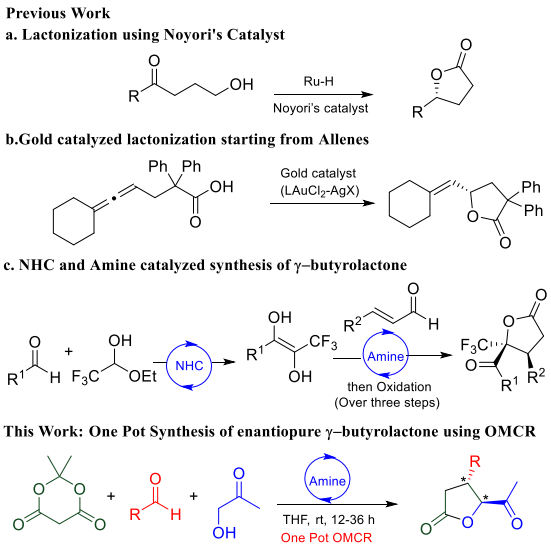

Figure 1. Enantioselective synthesis of γ-butyrolactones.

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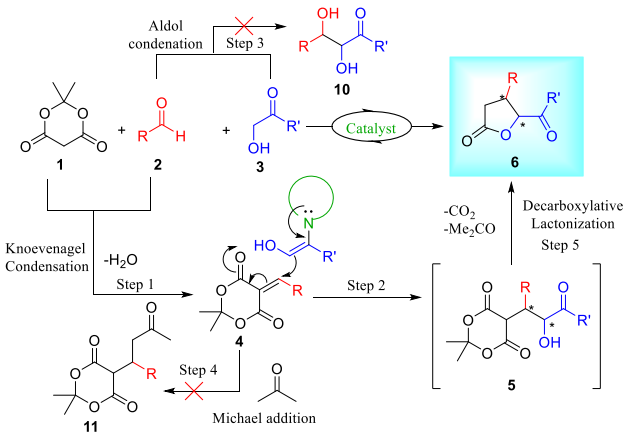
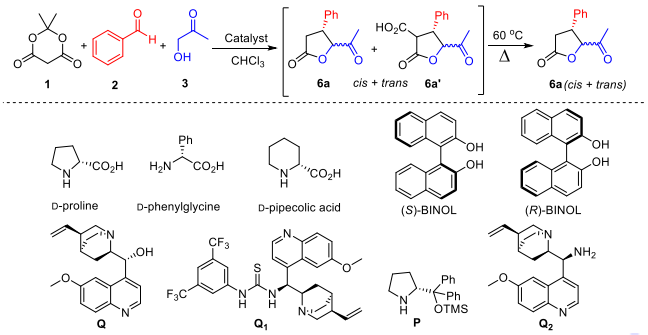
Remarkably, to the best of our knowledge, one-pot enantioselective organocatalytic multicomponent reaction (OMCR) for the formation of *γ*-butyrolactone remains an unmet challenge till date. Keeping all these parameters in mind, we ventured into developing a novel and more convenient strategy to synthesize *γ*-butyrolactone. Herein, in this paper we report a novel and expedient enantiopure synthesis of *γ*-butyrolactones achieved by organocatalytic enantioselective tandem three component reaction between Meldrum's acid, aldehyde and hydroxyketone for the first time. Recently our laboratory has shown a considerable interest in Meldrum's acid related synthesis.[7] In our continuing efforts, we became interested to evaluate the scope of Meldrum's acid with the asymmetric catalysis. Meldrum's acid has attracted significant attention as it offers various valuable products[8] and the usefulness of which is efficiently demonstrated in complex multicomponent processes.[9] Undoubtedly, *α,β*-unsaturated alkylidene Meldrum's acid derivative **4** acts as an excellent Michael acceptor in 1,4-addition reaction[10] and the ensuing intermediates are highly versatile compounds for various new transformations. By taking into account of these, we hypothesized a novel three component chemoselective tandem Knoevenagel-Michael-lactonization sequence as shown in scheme 1. However, our proposed multicomponent synthetic scheme has following daunting chemoselectivity challenges to be met (Scheme 1). Some of them are:(1) the Knoevenagel condensation reaction should rapidly lead to alkylidene Meldrum's acid product **4** (step 1); (2) very importantly, 1,4-Michael addition (step 2) has to be dominant over aldol condensation[11] (step 3); (3) by-product, acetone should barely take part in the reaction to avoid side product **11**[9a] (step 4), i.e. 1,4-Michael addition on intermediate **4**; (4) finally, the lactonization should happen in one pot (step 5) under ambient temperature. Keeping all these possibilities in mind, initially we planned to explore the reaction by using proline as a catalyst as it has widely been used in aminocatalysis.[12]



Scheme 1. Proposed one pot synthesis of enantiopure *γ*-butyrolactone via Knoevenagel-Michael-lactonization.

Initially, a model reaction was performed by using Meldrum's acid **1**, benzaldehyde **2a** and hydroxyacetone **3a** in presence of catalytic amount of D-proline (20 mol%) in chloroform. Gratifyingly, the desired lactone **6a** was obtained but as two separable diastereomers (1:2.1 *d.r.*), albeit in poor enantioselectivity at room temperature (Table 1, entry 1).



entry	Catalyst (mol%)	Additive (mol%)	Yield[b] (%)	*d.r.* (*trans*: *cis*) [c]	*ee* (%) (*trans*/ *cis*)[d]
1	D-Pro(20)	-	63	1:2.1	24/26
2[a]	D-Pro(20)	-	trace	nd	nd
3	D-Pro(20)	Q1(20)	64	1:2.1	nd/24
4	L-Pro(20)	Q1(20)	60	1:2.1	nd /21
5	L-Pro(20)	(*S*)-BINOL(20)	55	1:2	nd /25
6	L-Pro(20)	(*R*)-	50	1:2	nd /25
7	D-Phg(20)	Q1(20)	8	nd	nd
8	D-Pip(20)	-	trace	nd	nd
9	P (20)	-	-		-
10	-	Q1(20)	-	-	-
11	Q2(20)	-	70	2.5:1	89/
12	Q2(20)	TFA (40)	79	2.5:1	91/58
13[a]	Q2(20)	TFA (40)	trace	nd	nd
14[e]	**Q2(5)**	**TFA (10)**	**78**	**2.5:1**	**91/58**
15[e]	Q2(10)	TFA (20)	78	2.5:1	91/58

Reaction Conditions: Meldrum's acid **1** (1 equiv.), Benzaldehyde (1.05 equiv.), Hydroxyacetone (3 equiv.) Catalyst (5-20 mol%), Additive (10-40 mol%), in $CHCl_3$ at rt, 24 h, [a]reactions were carried out at 0 °C, [b]isolated yield after purification by column chromatography, [c]*dr* was calculated based isolated yileds [d]*ee* was determined by HPLC, [e]Reactions were stirred for 24 h followed by heating at 60 °C for 6 h for the decarboxylation.

The structures of both *cis* and *trans* diastereomers were confirmed by ^{1}H, ^{13}C NMR spectral analysis and single-crystal X-ray diffraction data (see ESI).[13] The low enantioselectivity of the product **6a** may be attributed to either inadequate steric bulk of proline or less efficient steric interactions. Initially, we believed that epimerization of *cis*-lactone would have resulted in poor diastereoselective outcome. However, this possibility was ruled out as we observed no epimerization of *cis*-lactone of **6a** under the similar reaction conditions even after prolonged reaction time. Subsequently, lowering the reaction temperature to 0 °C turned out to be extremely disadvantageous (Table 1, entry 2). This initial exciting breakthrough for the one pot lactonization encouraged us to screen some more efficient catalyst systems. Recently, it has been demonstrated that combining additional supplemental co-catalyst along with amino acids enhances the effective stereo interactions.[14] Therefore, we planned

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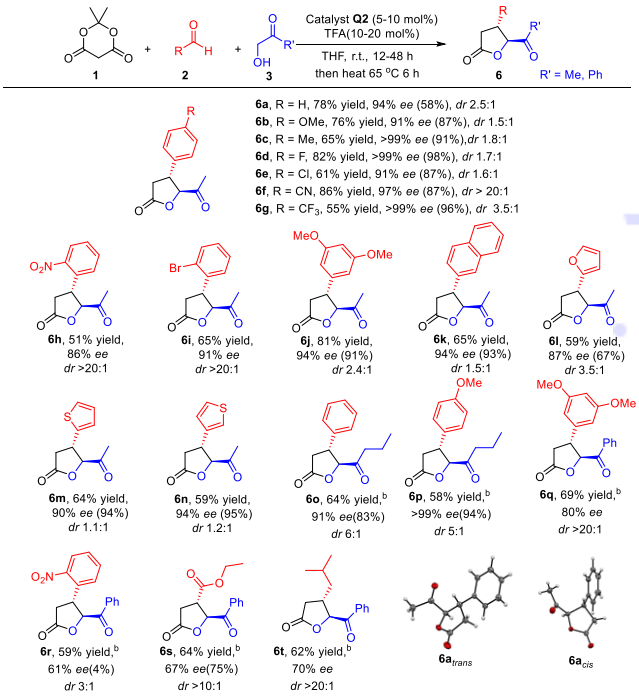
to introduce a cinchona based thiourea-amino acid catalytic assembly with an aim to have high stereocontrol to this reaction. However, all the modules did not enhance the enantioselectivity (Table 1, entries 3-7). The lack of enantioselectivity could be attributed to the unanticipated, but favorable acid-base interaction between Meldrum's acid (pKa 4.9) and thiourea. This might have resulted proline to catalyze the reaction solely. Surprisingly, additional amino acid based catalyst (D-pipecolic acid or P) and thiourea catalyst **Q1** were found to be extremely ineffective in terms of reactivity (Table 1, entry 8-10).

Based on these studies, we surmised that quinine based bifunctional diamine **Q2** may prove to be more potential to serve as a good catalyst. Chiral cinchona diamines are believed to invoke favorable stereo interactions due to their intrinsic ability to simultaneously form enamine and hydrogen bonding with high degree of conformational flexibility. To our delight, promising results were obtained in the presence of quinine based bifunctional primary amine catalyst **Q2** (20 mol%) by affording the desired product **6a** in 70% yield with good stereoselectivity (Table 1, entry 11). It is interesting to note that Knoevenagel condensation, Michael addition, lactonization and decarboxylation took place in one pot at room temperature to afford the desired product **6a**. While the two fold addition of TFA (40 mol%) along with the catalyst **Q2**(20 mol%) marginally enhanced the yield and enantioselectivity of desired product **6a** (Table 1, entry 12). Presumably, TFA might have reduced the unanticipated acid-base interaction between catalyst **Q2** and Meldrum's acid. Further reduction in catalytic loading (5 and 10 mol%, entries 14, 15) afforded the desired product **6a** along with the undecarboxylated intermediate **6a'** (detected by HRMS) at room temperature (see Table 1, entries 14, 15), unlike in case of higher catalytic loading (20 mol%) wherein, decarboxylation took place without heating (see Table 1, entry 12). We observed the incomplete decarboxylation even after prolonged reaction time (48 h). Further, in order to decarboxylate the intermediate **6a'**, the reaction mixture was heated at 60 °C for 6 h for the complete decarboxylation to afford product **6a** in 78% yield without any erosion of enantioselectivity (91% *ee*). Based on these results, to avoid higher catalytic loading, we decided to use 5 mol% of catalyst **Q2** followed by heating for the substrate scope. Encouraged by the initial results, further we screened various solvents under optimized reaction condition (**Q2** 5 mol% followed by heating, see ESI). Interestingly, THF was found to be the best solvent for the desired transformation (**6a**, 78% yield, 94% *ee*). On the other hand polar solvents such as H_2O, DMSO, DMF, EtOH had a detrimental effect on the reaction.

Having obtained the optimized reaction conditions in hand (5 mol% **Q2**, 10 mol% TFA in THF at room temperature for 24 h followed by heating at 65 °C for 6 h in one pot), further the scope of Knoevenagel-Michael-lactonization was investigated using various aldehydes and hydroxyketones. It was observed that aromatic aldehydes containing electron donating as well as withdrawing functional groups reacted smoothly under the optimized reaction conditions to afford the corresponding lactones (**6b-6j,** Table 2) in good yields with high to excellent enantioselectivity (up to 99% *ee*). Naphthaldehyde under the reaction conditions afforded the corresponding lactone **6k** in good yield and excellent enantioselectivity (65%, 94% *ee*).

Table 2. One pot enantiopure synthesis of γ-butyrolactones[a-e]



[a]Reaction conditions: Meldrum's acid **1** (1 equiv.), Aldehyde (1.05 equiv.), Hydroxyketone (3 equiv.) **Q2** (5 mol%), TFA as additive (10 mol%), in THF at rt, 24 h then heat at 65 °C in one pot; [b]10 mol% of catalyst **Q2** and TFA (20 mol%) were used for the complete conversion, [c]isolated yield after purification by column chromatography, [d]*d.r.* was calculated based on isolated yields [e]*ee* was determined by HPLC; *ee* of *cis*-isomer is given in parenthesis.

Similarly, heteroaromatic aldehydes such as furfural and thiophene 2/3-aldehydes afforded the corresponding lactones **6l**, **6m** and **6n** respectively (up to 94% *ee*, Table 2). In order to have generality of the method and for the wider practicability, we planned to explore the reactions of 1-hydroxy-2-pentanone **3b** and 2-hydroxyacetophenone **3c.** Under the optimized reaction conditions **3b** reacted smoothly with aldehydes **2a**, **2b** and Meldrum's acid **1** to afford the corresponding lactones **6o** and **6p** in moderate to good yields with excellent enantioselectivity (see, Table 2). Likewise, the reaction of 2-hydroxyacetophenone **3c** with aldehydes **2j** and **2h** afforded the corresponding products **6q** and **6r** respectively in moderate to good yield with good enantioselectivity. Interestingly, it is very significant to note that the reaction of aliphatic aldehydes such as isovaleraldehyde **2o** and ethyl glyoxalate **2p** with 2-hydroxyacetophenone afforded the corresponding lactones **6s** and **6t** in good enantioselectivity. We observed that steric and electronic factors did not have any significant effect on the efficiency and yield of the reaction. Wide variety of aldehydes and different functional groups tolerated the reaction conditions. In order to have some insight into stereochemical outcome of the transformation and mechanistic aspects, we carried out few experiments

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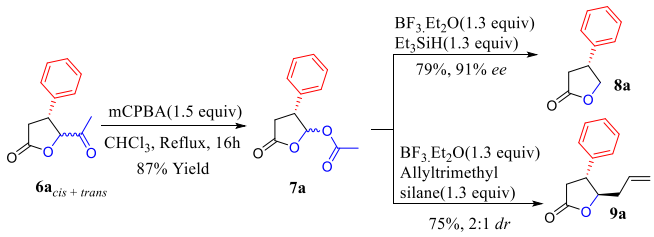
on lactone **6b**. Esterification followed by oxidation of two separate diastereomers of **6b** (*cis* and *trans*) afforded the corresponding identical enantiomer (see ESI). This revealed that only one face of alkylidene Meldrum's acid **4** interacted with the both *re* and *si* face of hydroxyacetone enamine (**ENM**). To assign the absolute configuration, the product **6a**$_{cis+trans}$ was subjected to Baeyer-Villiger oxidation followed by reduction of **7a** (Scheme 2). By comparing the specific rotation of product **8a** with the literature value, the absolute configuration of **6a** was assigned as '*R*' at benzylic position (observed specific rotation $[\alpha]_{25}^{D} = -41.0$ (*c* 1.0, $CHCl_3$), literature $[\alpha]_{23}^{D} = -27.7$ (*c* 4.0, $CHCl_3$) for '*R*' configuration).[15]

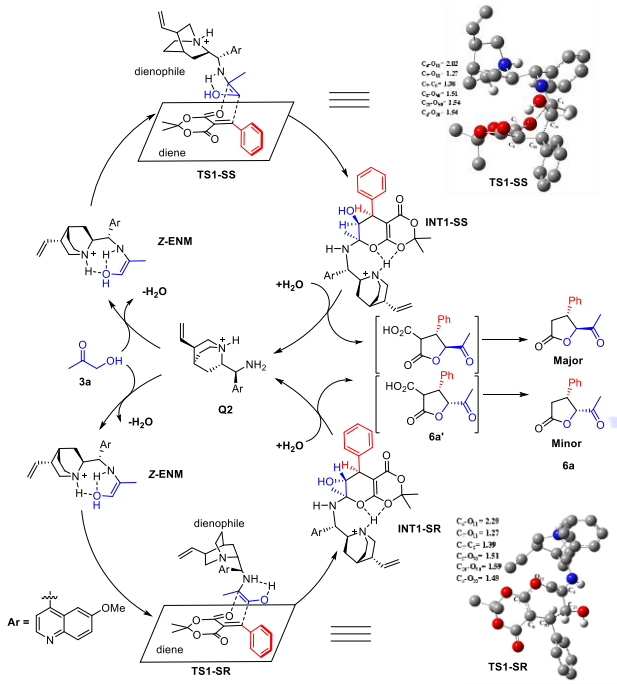


Scheme 2. Reduction and allylation of butyrolactone **6a.**

Further, to make this protocol more practical and to demonstrate the synthetic utility of the products, synthetically useful allyl lactone **9a** was synthesized starting from compound **7a** in a shorter pathway. Further, to demonstrate the practical utility of this protocol, lactone **6a** was synthesized on a gram scale in good yield (75%) without the erosion of enantioselectivity (94% *ee*) (Scheme 2).

To have a better understanding of the mechanism and stereoselectivity of reaction catalyzed by chiral cinchona catalyst **Q2**, we planned to investigate the intermediates and transition states (TS) that are involved in the catalytic cycle by Density Functional Theory (DFT) calculations. The proposed catalytic cycle is outlined in Scheme 3. Initially protonated primary amine **Q2** catalyzes Knoevenagel condensation to afford the corresponding heterodiene **4a**. Further this reacts with enamine (***Z*-ENM** and ***E*-ENM** as dienophile) via [4+2]-hetero-Diels-Alder cycloaddition pathway. DFT calculations revealed that *Z*-enamine (***Z*- ENM**) is 7.059 kcal.mol^{-1} more stable than *E*-enamine (***E*-ENM**) due to favorable hydrogen bonding. It is important to note that under experimental conditions, we obtained only *RS* and *RR* lactones selectively.

The optimized structures of all the reactants, TS's, intermediates and products are given in ESI. Calculations were carried out to determine the role of TS's on the outcome of stereochemistry of the lactones. This was further unambiguously supported by single crystal X-ray analysis and specific rotation. Keeping this in view, we computationally studied the attack of only ***Z*-ENM** (both *re* and *si faces*) to the only *si* face of heterodiene **4a** in detail for the outcome of *RS* and *RR* lactones (see ESI for data and details). Transition state TS1-*SS* (*si* face of **4a** and *si* face of ***Z*-ENM**) is 5.534 kcal.mol^{-1} more stable than TS1-*SR* (*si* face of **4a** and *re* face of ***Z*-ENM**). TS1-*SS* leads to more stable major product lactone **6a**-*RS* (10.69 kcal.mol^{-1} more stable than **6a**-*RR* lactone) through a series of transition states and intermediates for the stepwise mechanism (see ESI).



Scheme 3: Proposed catalytic cycle. [a,b,c]
[a]Selected bond distances are in Å. [b]Relative free energies given in kcal·mol^{-1}; M06-2X/6-311++G(d,p)/SMD//M06-2X/6-31G(d). [c]Most of the H-atoms have been omitted for the sake of clarity.

These DFT calculations strongly support the experimental results and high stereoselectivity (Theoretical *ee* = 99% is in very good agreement with the experimental *ee* = 94%).

In conclusion, we developed a novel, robust and a straightforward protocol for the highly enantiopure synthesis of γ-butyrolactones via one-pot organocatalytic multicomponent reaction (OMCR) strategy. Potential of OMCR is explored for the first time for the rapid access of enantiopure lactone scaffolds starting from commercially available simple starting materials. Experimental observation was further supported by the computational studies. More importantly protocol avoids the use of pre-functionalized substrates, additional base and, expensive transition metals. Reaction proved to be highly enantioselective and reproducible on a gram scale and is proved to practical to access synthetically useful lactones.

Experimental Section

In a glass vial equipped with a teflon-coated stir bar, 9-amino(9-deoxy)*epi*quinine **Q2** (0.07 mmol, 22.4 mg, 10 mol%) was dissolved in 1.0 mL of THF. After addition of TFA (0.14 mmol, 10.6 µL, 20 mol%), the reaction mixture was stirred for 15 minutes. Then Meldrum's acid 1 (100 mg, 0.7 mmol, 1 equiv.), benzaldehyde (74.3 µL, 0.73 mmol, 1.05 equiv.) and hydroxy acetone (145.6 µL, 2.1 mmol, 3 equiv.) were added subsequently and stirred for 12 h or as indicated in the manuscript. Upon complete consumption of Meldrum's acid, the reaction mixture was heated at 65 °C for 6 hours to decarboxylate the acid intermediate. The crude product **6a** was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as an eluent. Compound **6a** was obtained as solid in 78% yield.

Acknowledgements

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