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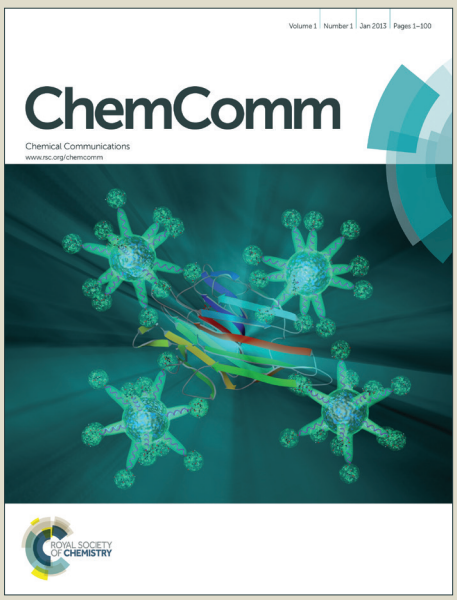

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Asymmetric Vinylogous Michael Reaction of Cyclic Enones with Silyloxy Furnas

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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The asymmetric vinylogous Michael reaction of cyclohexenone/ medium and large cyclic enones with 2-silyloxyfuran is still a synthetic challenge. In this report, we have explored an enantioselective chiral, primary diamine catalyzed, 2-silyloxy furan's 1,4-conjugate addition to various cyclic enones and β-substituted cyclic enones. The reaction provided *syn*-Michael adduct (cycloalkane connected γ-butenolide) with good yields, diastereo- and enantioselectivities. Further, the synthetic potential of these *syn*-Michael adducts is demonstrated by 1,4-addition of nucleophiles on the butenolide substructure.

Chiral *γ*-butenolide and their derivatives are ubiquitous architectural subunit of numerous natural products[1] and also serve as important building blocks for the synthesis of biologically active compounds.[2] Particularly, cycloalkane connected γ-butenolides with chiral quaternary center at cycloalkane-connecting point is of great interest (Fig 1).[3] Owing to the built-in steric repulsion, the asymmetric installation of quaternary all-carbon stereogenic centres remains a difficult and imperative problem in chiral catalysis and has been a domain of large research interest in synthetic organic chemistry.[4] One of the approaches towards this objective, the asymmetric conjugate addition of carbon based nucleophiles to β, β′-disubstituted acceptors, facilitates the synthesis of quaternary carbon containing adducts. Significant effort has been made for the synthesis of quaternary centers by the asymmetric conjugate addition of highly reactive organometallic reagents to various acceptors such as acyclic and cyclic enones in presence of copper catalysts.[5] However, very few organocatalytic reactions of such sterically hindred β,β′-di-substituted acceptors with C-nucleophiles have been reported until now.[6] In addition, the reported methodologies are extremely limited in scope and have been applied only to some common reactions like the Diels-Alder,[7] Friedel-Crafts,[8] Stetter,[9] organocatalytic hydrogenation,[10] epoxidation[11] and aziridination reactions.[12] Other interesting asymmetric reactions such as the Vinylogous Michael (VM) reaction of the corresponding nucleophiles to the β,β′-disubstituted enones, which can yield a stereogenically rich chiral quaternary center containing functionalized carbon backbone are still unexplored. In fact, the VM reactions reported so far are practically limited to *β*-monosubstituted α,β-unsaturated carbonyl compounds and nitroalkenes.[13] Although, progress has been made for the catalytic asymmetric Michael reactions of furanone to simple enones, number of critical issues related to structural constrains of the acceptor remain unresolved. Moreover, the catalytic asymmetric Michael reactions of functionalized nucleophiles such as 2-silyloxyfuran and furanone to β, β′-disubstituted enones is yet unexplored. It is noteworthy that though challenging, the transformation of β-substituted cyclic enones, if achieved efficiently in large rings, can deliver products that can be used in enantioselective synthesis of a variety of biologically active natural products.

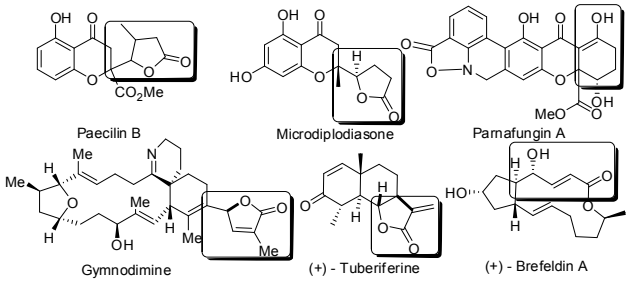

Fig.1 Natural products containing carbocyclic core connected with *γ*-butenolide/*γ*-lactone or derived framework as substituent

Previously reported approaches for asymmetric vinylogous Michael

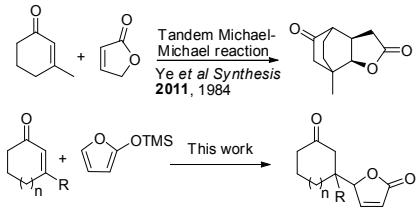

Fig. 2. Challenging substrate class for asymmetric vinylogous Michael reaction

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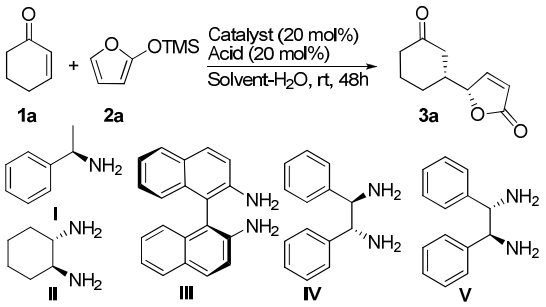
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

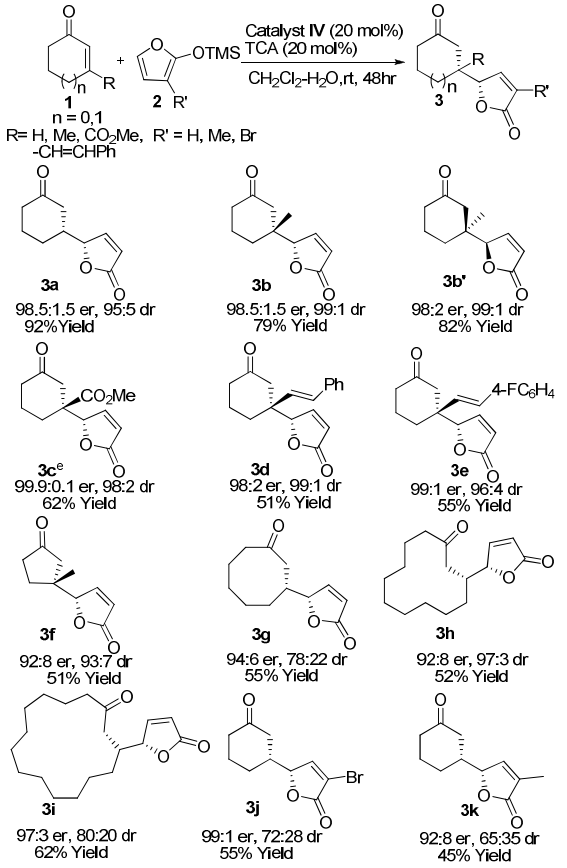
Table 1. Catalyst screening and optimization of asymmetric vinylogous Michael reaction of cyclohexenone with 2-silyloxyfuran[a]



entry	Catalyst	Acid	Solvent	Yield[b] (%)	dr[c] (*syn*/*anti*)	er[d] (*syn*)
1	**I**	TFA	CH_2Cl_2	27	81:19	88.5:11.5
2	**II**	TFA	CH_2Cl_2	39	99:1	52:48
3	**III**	TFA	CH_2Cl_2	-	-	-
4	**IV**	TFA	CH_2Cl_2	38	80:20	92.5:7.5
5	**IV**	AcOH	CH_2Cl_2	36	91:9	91:9
6	**IV**	TfOH	CH_2Cl_2	28	83:17	65:35
7	**IV**	PNBA	CH_2Cl_2	75	94:6	97.5:2.5
8	**IV**	TCA	CH_2Cl_2	92	95:5	98.5:1.5
9	**IV**	2,4-DNBA	CH_2Cl_2	89	94:6	98.5:1.5
10[e]	**IV**	TCA	CH_2Cl_2	82	77:23	98:2
11	**IV**	TCA	THF	38	77:23	96.5:3.5
12	**IV**	TCA	Et_2O	47	89:11	94:6
13	**IV**	TCA	1,4-Dioxane	78	92:8	98:2
14[f]	**IV**	TCA	CH_2Cl_2	85	77:23	98:2
15	**V**	TCA	CH_2Cl_2	90	92:8	1.5:98.5[g]

[a]All reactions were performed with 1 equiv. of **1a** (0.20 mmol), 1.5 equiv of **2a** (0.30 mmol), 0.20 equiv of catalyst (0.04 mmol) and 0.20 equiv of acid (0.04 mmol) in 1.0 mL of CH_2Cl_2 and 20 μL of H_2O. [b] Isolated yield. [c] Determined by HPLC analysis and/or ^{1}H NMR analysis. [d]Determined by HPLC analysis. [e]Acid additive 1.5 equivalent. [f] With 50 μL of water. [g]Enantiomer **3a'** (see SI).

Table 2. Organocatalytic asymmetric vinylogous Michael reaction of various cyclic enones with 2-silyloxyfurans and substituted 2-silyloxyfurans [a,b,c,d]



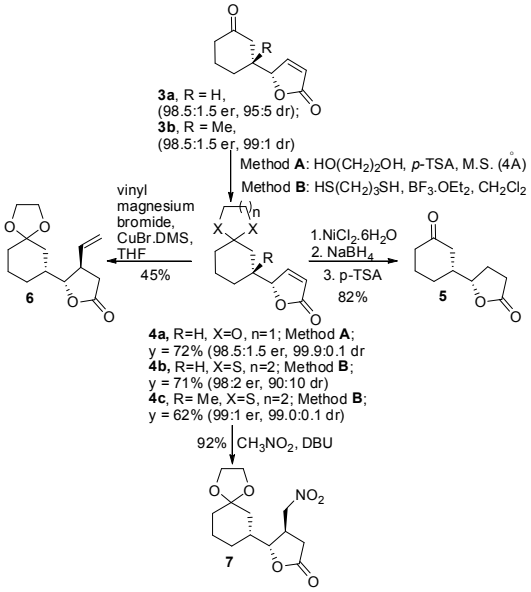
[a] Reactions were performed with 1 equiv. of **1a-k** (0.20 mmol), 1.5 equiv of **2a-c** (0.30 mmol), 0.20 equiv of catalyst (0.04 mmol) and 0.20 equiv of acid (0.04 mmol) in 1.0 mL of CH_2Cl_2 and 20 μL of H_2O. [b] Isolated combined yield of vinylogous Michael adducts **3a-k**. [c] Determined by HPLC analysis and/or ^{1}H NMR analysis. [d] Determined by HPLC analysis. [e] 30 mol% of catalyst and acid loading.

reaction of γ-butenolide to α, β-unsaturated ketones are only restricted to chalcones, acyclic enones, and to five- and seven-membered cyclic enones.[14] Interestingly, there are no reports of γ-butenolide addition to six-membered cyclic enone. In fact, it has been reported that the addition of γ-butenolide to β-substituted cyclohexenone, yielding the tricyclic lactone directly, results in a tandem Michael-Michael reaction.[15] Herein, we disclose the development of a simple, commercially available chiral organic catalyst system that effectively promotes the *syn*-selective asymmetric vinylogous Michael reactions of various 2-silyloxyfurans with cyclic enones and 3-substituted cyclic enones. As chiral amine catalyzed asymmetric Michael reactions of enals and enones are well established in literature,[16] we started our investigations by examining the ability of various chiral amines to promote the vinylogous Michael reaction for our model substrates, cyclohexenone **1a** and 2-silyloxyfuran **2a** (Table 1).

In an exploratory effort, we applied 20 mol% of amine catalyst, 20 mol% TFA as co-catalyst and 20 μL water. We realized that Michael reaction proceeded to give **3a** in low yield and with poor diastereoselectivity and enantiomeric ratio in presence of chiral primary monoamine **I** (entry 1, table 1). Since, diamines can activate both enone and 2-silyloxyfuran *via* iminium ion formation and hydrogen bonding respectively; we sought out to explore vinylogous Michael reaction with chiral 1, 2-diamino cyclohexane **II**, BINAP **III** and 1,2-diphenylethylene diamine **IV**. We found that cyclohexyl diamine gave moderate yield but low enantioselectivity (entry 2, table 1). Interestingly, the reaction with BINAP did not result in any product (entry 3, table 1). On the other hand, 1,2-diphenyl ethylene diamine gave reasonably good yield and selectivity (entry 4, table 1). We also observed that an acid additive is needed for the reaction, thus, indicating that ketiminium probably serves as a key intermediate. A thorough investigation of acid additives including TFA, CH_3COOH, TfOH, PNBA, TCA and 2,4-DNBA revealed that TCA gave better yield and selectivity (entry 5 to entry 9, table 1). Also, one equivalent of acid additive was found to be necessary for achieving excellent yield and selectivity. Increasing the acid additive (1.5 equiv) reduced the diastereoselectivity (77:23) (entry 10, table 1). While screening for the solvents, it was observed that methylene chloride was most efficient (entry 11 to 13, table 1). Lowering of temperature to 0°C slowed down the reaction drastically. Hence, all the reactions were carried out at room temperature. We would also like to mention that the volume of water added in the reaction was crucial in governing the yield and *er* of the reaction. Increasing the volume of water to 50 μL resulted

in decrease in the yield and *dr* dramatically (entry 14, table 1). We were glad to notice that unlike in the literature, only 5-10% of the double Michael adduct was observed in the optimized condition.[15]

Having established the optimal reaction conditions (entry 8, Table 1), we next probed the scope and limitations of this enantioselective vinylogous Michael addition reaction with regard to various cyclic enones as well as 2-silyloxy furans. We first investigated the feasibility of various cyclic enones with varying the substituent at the β-position and the ring size using 2-silyloxyfurans as a nucleophile. Indeed, treating different cyclic enones with 2-silyloxyfuran (1.5 equiv) in the presence of the catalytic amine **IV** (20 mol%), at room temperature for 48-96 hours gave the corresponding adducts **3** in good yields, diastereo- and enantioselectivities in almost all cases studied (Table 2). In the case of β-substituted cyclohexenones, having methyl, 3-oxo-methyl ester, styryl and 4-F-styryl substitution, all gave excellent diastereo- and enatioselectivities and good yields (Table 2, **3b-3e**). Using the enantiomeric catalyst **V** of the diamine catalyst **IV**, the opposite enantiomeric product **3a'** and **3b'** were obtained with almost same conversion and selectivity. β-substituted cyclopentenone too gave excellent distreo- and enantioslectivity albeit with moderate yield (Table 2, **3f**). Gratifyingly, eight, twelve and fifteen membered cycloalkenones all underwent asymmetric vinylogous Michael reaction with good yields and high enantioselectivities. However, the *dr* was lower for eight membered and fifteen membered cyclic enones, whereas, twelve membered gave excellent diastereomeric ratio (97:3) (Table 2, **3g- 3i**). We also investigated the reaction of cyclohexenone with 3-substituted-2-silyloxy furans. The reaction gave Michael adducts with excellent enantioselectivitiy but with the erosion of the distereoselectivity and with moderate yields (Table 2, **3j** and **3k**).



Scheme1. Transformation of vinylogous Michael adducts **3a** and **3b**

The excellent substrate scope of the developed VM reaction encouraged us to probe the synthetic utility of the adduct **3a**. We carried out multiple transformations as illustrated in Scheme 1. The ketal and thioketal protection of **3a** and **3b** by ethylene glycol and 1,3-propanedithiol respectively yielded **4a**, **4b** and **4c** in good yield without any major loss in selectivity. Further, the α, β-unsaturated lactone in **4a** was easily reduced with $NiCl_2.6H_2O/NaBH_4$ to yield a ethyleneketal protected lactone **4d**, which was further deprotected in presence of catalytic *p*-TSA to yield the cyclohexanone connected saturated lactone **5**. The 1,4-vinylation of **4a** with mono vinyl copper yielded lactone **6**. The 1,4-addition of nitromethane to **4a** yielded adduct **7**.

Finally, we confirmed the relative and absolute configuration of the vinylogous Michael adduct by X-ray crystal structure analysis of

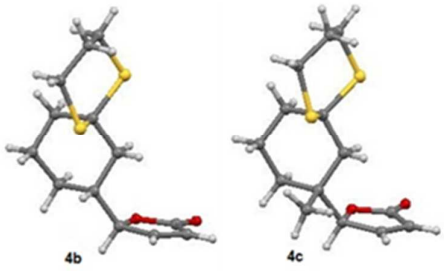


Fig. 3 X-ray structures of products **4b** and **4c**

a dithioketal derivative **4b** and **4c** of **3a** and **3b**. The relative configuration of the major stereoisomer of Michael adduct was established to be *syn* (see Supporting information (SI)). Based on these observations, we hypothesized a transition state for **IV**-promoted vinylogous Michael reaction illustrated in scheme S1 (see SI).

We have developed a primary diamine-catalyzed *syn*-selective asymmetric vinylogous Michael reaction of 2-silyloxyfurans to cyclic enones. Synthetically versatile cycloalkanones connected γ-butenolides with contiguous tertiary followed by quaternary stereocenter were prepared stereoselectively. Efforts towards developing a more efficient catalyst to include less reactive 5-substituted silyloxyfurans and cyclic enones for stereoselective generation of two contiguous quaternary stereocenters in Michael adduct is currently underway in our laboratory.

We are grateful for the generous financial support from DST-India (SR/S1/OC-83/2012). APJ and VUBR thank CSIR-New Delhi for the award of a Senior Research Fellowship. PKS thanks UGC for the Junior Research Fellowship. RPS thanks to Indian Institute of Technology-Delhi (IRD and Planning Unit) for a generous start up grant. We thank DST-FIST for Mass Spectrometer facility.

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