With representation in over 13,000 natural products, the γ-butenolide synthone has become a valuable architectural platform for the development of new asymmetric methodologies. In this context, the catalytic coupling of silyloxy furans and aldehydes using chiral Lewis acids has emerged as a prominent strategy for γ-butenolide synthesis (eq 1), further outlining the broad utility of the Mukaiyama–Aldol transform in asymmetric synthesis. Surprisingly, however, the analogous 1,4-addition of silyloxy furans to electron deficient olefins (eq 2) has received relatively little attention despite the numerous examples of 5-(1-alkyl)-5-H-furane stereogenicity found among natural isolates (e.g., kallolide). This deficiency in Mukaiyama–Michael technology may arise, in part, from the documented selectivity of metal salts to promote 1,2-formyl activation in preference to 1,4-olefin addition with ambident electrophiles such as α,β-unsaturated aldehydes. In this communication, we reveal that iminium organocatalysis using chiral imidazolidinones has overcome such limitations to provide the first enantioselective Mukaiyama–Michael reaction with simple unsaturated aldehydes. Importantly, this strategically new approach to asymmetric γ-butenolide construction further serves to highlight the complementary mechanistic function of LUMO-lowering iminium and metal catalysis and the chemical utility of enantioselective organocatalysis.

Our enantioselective organocatalytic butenolide synthesis was first examined using silyloxy furan, imidazolidinone catalyst 1, and crotonaldehyde (Table 1). Preliminary studies revealed that the proposed conjugate addition was indeed possible with excellent levels of syn diastereoselectivity and enantiocontrol (entry 1, 10:1 syn:anti, 85% ee; however, catalytic efficiency was poor (31% yield). On the basis of the assumption that imidazolidinone turnover was being inhibited by loss of H2O from the catalytic cycle (presumably via formation of (TMS)2O), we next examined the use of protic additives that might competitively scavenge the putative silyl cation intermediate. While a variety of alkyl alcohol additives were found to be productive in this context (entries 2–5), the addition of excess H2O (2 equivs) provided optimal reaction efficiency (entries 5 and 6, ≥84% yield) and stereoselectivities at −70 °C (entry 6, syn:anti 22:1, 92% ee). The superior levels of asymmetric induction and efficiency exhibited by the amine salt 1-2,4-dinitrobenzoic acid (DBNA) in CH2Cl2−H2O to afford the stereochemically enriched butenolide (R)-4 in 92% ee prompted us to select these catalytic conditions for further exploration.

Experiments that probe the scope of the α,β-unsaturated aldehyde component are summarized in Table 2. There appears to be significant latitude in the steric demands of the β-olefin substituent (entries 1–4, R = Me, Pr, i-Pr, Ph) to enable access to a broad variety of 5-(1-alkyl)-5-methyl-furanones (syn:anti 7:1 to 31:1, 84–99% ee). Moreover, variation in the electronic nature of the aldehyde component has apparently little influence on the relative or absolute sense of stereoinduction. For example, optimal levels of asymmetric induction are available with enals that do not readily participate in iminium formation (entry 6, R = CO2Me, 84% yield, 99% ee), as well as aldehydes that provide stable iminium intermediates (entry 4, R = Ph, 77% yield, 99% ee). In accord with our mechanistic postulate, it is important to note that products arising from 1,2-iminium addition were not observed with all of the aldehydes examined.
Significant structural variation in the silyloxy furan system can also be realized (Table 3). Importantly, the reaction appears quite tolerant with respect to the substituent at the furanyl 5-position (entries 1–4, R = H, Me, Et, CO₂Me 90–92% ee). While high levels of syn,5′-stereogenicity are available in the construction of a wide variety of γ-butenolide systems (entries 1–4, 6), the corresponding anti isomer can also be forged with excellent levels of stereoelectivity via the appropriate selection of cocatalyst and solvent (entry 5, syn:anti 1:7, 98% ee, 83% yield). Moreover, the introduction of alkyl substituents at C(3) on the furan ring can also be accommodated without loss in diastereocontrol or enantioinduction (entry 6, syn:anti 24:1, 98% ee).

A demonstration of the utility of these enantioselective organocatalytic silyloxy furan additions and the accompanying butenolide products is presented in the four-step synthesis of spiculisporic acid (5).²⁰,²¹ A *Penicillium spiculisporum* fermentation adduct has found commercial application as a biosurfactant for (i) metal decontamination processes and (ii) fine polymer production.²⁴ As revealed in eq 3, treatment of tert-butyl 4-oxobutenoate (7) with 2-triisopropylsilyloxy carbamothioxy furan (6) in the presence of 20 mol % of (2R,5R)-amine salt 1-TFA in THF provides the stereochemical core of spiculisporic acid 8 in one step, 90% yield, 11:1 syn:anti selectivity and 89% ee. Elaboration of butenolide 8 to spiculisporic acid was accomplished in 54% overall yield using a three-step procedure (see Supporting Information). Significantly, we have found that treatment of methyl 4-oxobutenoate (9) with furan 6 in the presence of the TfOH salt of catalyst 1 provides the opposite sense of diastereinduction, while retaining excellent levels of enantiocontrol in the production of the anti-5,5′-butenolide 10 (eq 4, 22:1 anti-syn, 97% ee). Importantly, this adduct can also be efficiently converted in three steps to 5-epi-spiculisporic acid (11),²⁵ a butenolide that is not readily available via fermentation protocols or derivatization of the naturally occurring metabolite. Studies to characterize the physical and material properties of 5-epi-spiculisporic acid are now underway.

With regard to the synthetic and operational advantages of the organocatalytic Mukaiyama—Michael, it is important to note that (i) the sense of asymmetric induction observed in all cases was readily anticipated by the previously described computational model MM3-2 and (ii) all of the conjugate additions described herein were performed under an aerobic atmosphere, using wet solvents and an inexpensive bench-stable catalyst. In summary, we have further established iminium catalysis as a valuable strategy for asymmetric synthesis in the context of the first enantioselective catalytic Mukaiyama—Michael addition using simple α,β-unsaturated aldehydes. A full account of this survey will be forthcoming.
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Supporting Information Available: Experimental procedures, structural proofs, and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References
(1) This number is based on a survey of the Beilstein database.

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