Communication

Direct Enantio- and Diastereoselective Vinylogous Addition of Butenolides to Chromones Catalyzed by Zn-ProPhenol

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Direct Enantio- and Diastereoselective Vinylogous Addition of Butenolides to Chromones Catalyzed by Zn-ProPhenol

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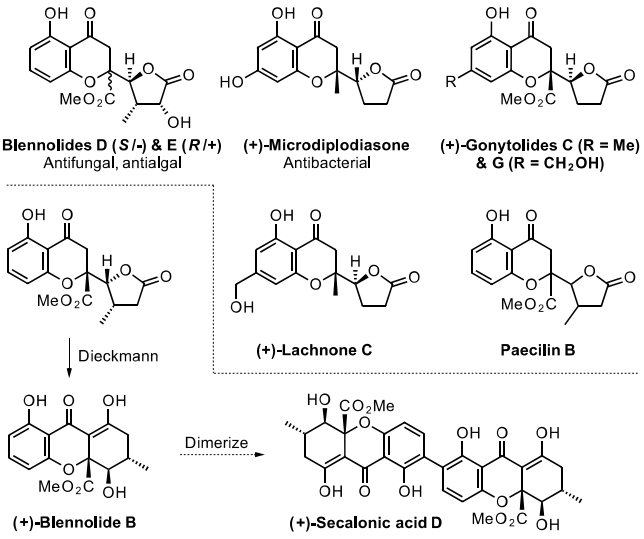
Supporting Information Placeholder

ABSTRACT: We report the first enantio- and diastereoselective 1,4-addition of butenolides to chromones. Both α,β- and β,γ-butenolide nucleophiles are compatible with the Zn-ProPhenol catalyst, and pre-activation as the siloxyfurans is not required. The scope of electrophiles includes a variety of substituted chromones, as well as a thiochromone and a quinolone, and the resulting vinylogous addition products are generated in good yield (31 to 98%), diastereo- (3:1 to >30:1), and enantioselectivity (90:10 to 99:1 er). These Michael adducts allow rapid access to several natural product analogs, and can be easily transformed into a variety of other interesting scaffolds as well.

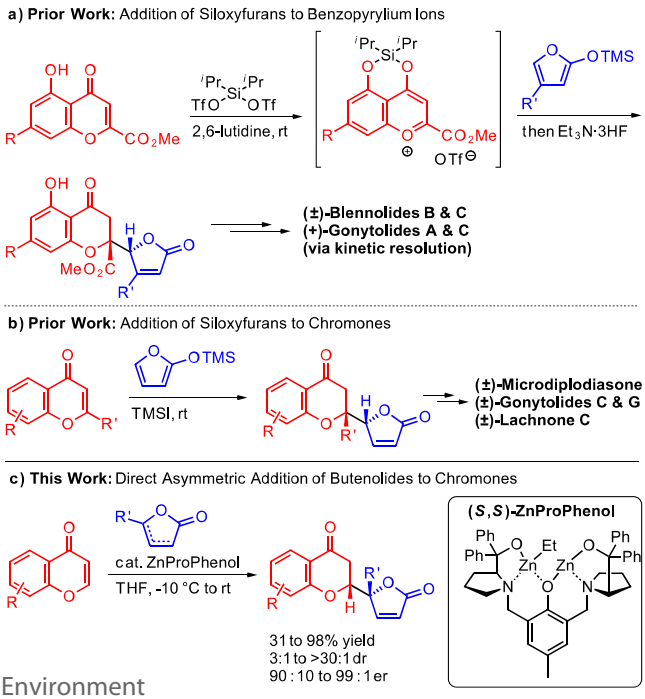
The chromanone lactones are a class of natural products consisting of 4-chromanones bearing a five-membered lactone at the 2-position. Comprised of no less than three dozen members,[1] this family of natural products includes several biologically active molecules (Scheme 1). For example, blennolides D and E have antifungal and antialgal properties,[2] and microdiplodiasone inhibits the bacteria responsible for Legionnaires' disease.[3] In light of their structural diversity and biological activity, it is no surprise that the total synthesis of chromanone lactone natural products has been an active area of research.[4] In addition to being attractive synthetic targets themselves, chromanone lactones can also be used as synthetic intermediates to access tetrahydroxanthone natural products, many of which also have interesting biological properties.[5] To this end, Porco and coworkers demonstrated that Dieckmann condensation of chromanone lactone **1** generates blennolide B,[4a] which is the monomeric unit of secalonic acid D. The latter compound has antimicrobial properties,[6] and is also a topoisomerase inhibitor with potential anticancer applications.[7]

Scheme 1. Chromanone Lactones in Natural Products and as Synthetic Intermediates.



The asymmetric preparation of butenolide-containing molecules is of broad interest for natural product synthesis.[8] More specifically, the vinylogous addition of butenolides (or their synthetic equivalents) to chromones is an attractive strategy for accessing chromanone lactones and while this method has been used to synthesize several natural products, an asymmetric version of this transformation is completely unknown. Taking advantage of the 5-hydroxy substitution that is often present in naturally occurring chromanone lactones, Porco *et. al.* developed a method whereby benzopyrylium ions generated *in situ* from 5-hydroxychromones are trapped by siloxyfurans (Scheme 2a). The resulting adducts were carried forward into concise total syntheses of (±)-blennolides B and C,[4a] as well as syntheses of (+)-gonytolides A and C that relied on a kinetic resolution to set the absolute stereochemistry.[4j] Based on an initial observation by Brimble,[9] Li and Zhang developed a moderately diastereoselective vinylogous addition of siloxyfurans to chromones promoted by TMSI (Scheme 2b). Using this strategy, the authors were able to complete total syntheses of (±)-microdiplodiasone, (±)-gonytolides C and G, and (±)-lachnone C.

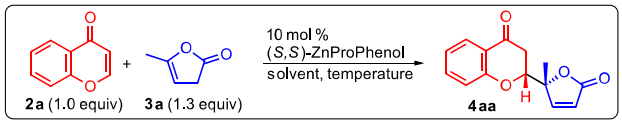
Scheme 2. Summary of Prior and Current Work.



As evidenced by the examples presented in Scheme 2a-b, the 1,4-addition of activated butenolides to chromones is a well-precedented and direct strategy for synthesizing chromanone lactone natural products, but the lack of an enantioselective variant is a major limitation. Given our recent success using Zn-ProPhenol to catalyze the asymmetric addition of butenolides to both aldimines[10] and ketimines,[11] we were curious to see whether we could use this catalyst to promote the enantioselective addition of butenolides to chromones. We anticipated this would be a challenging transformation. Although we knew that butenolide nucleophiles were well-suited for ProPhenol catalysis, we were less confident about using chromones as electrophiles. While the use of Zn-ProPhenol to catalyze 1,2-additions to aldehydes and imines[12] is well established, ProPhenol-catalyzed 1,4-addition reactions are much less common.[13]

To initiate our studies, we treated chromone **2a** with α-angelica lactone **3a** in the presence of 10 mol % Zn-ProPhenol in toluene. Remarkably, Michael adduct **4aa** was obtained as the sole product in 70% NMR yield with moderate dr and er (Table 1, entry 1). With halogenated solvents (entries 2 and 3) or ether (entry 4), both the yield and selectivities were lower than in toluene. Fortunately, THF gave significantly better results, and **4aa** was obtained in a much-improved 77% yield, 14:1 dr, and 93:7 er (entry 5). Lowering the temperature to 4 °C improved both the diastereo- and enantioselectivity without impacting the yield (entry 6). Interestingly, the addition of molecular sieves gave a slightly better yield of **4aa**, though the diastereoselectivity dropped precipitously (entry 7). Attempts to improve the enantio- and diastereoselectivity using non-C2-symmetric ProPhenol ligands[14] were unsuccessful (Table S1), but further lowering the temperature to -10 °C was beneficial (entry 8) and furnished **4aa** in 75% isolated yield with 16:1 dr and 97.5 : 2.5 er.

Table 1. Reaction Optimization.[a]

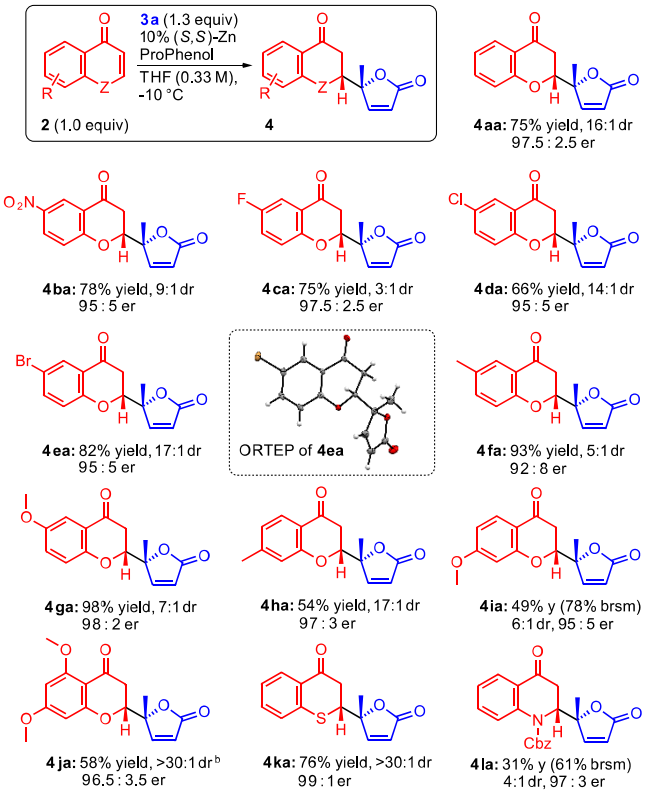


entry	solvent	*T*	yield (%)	dr	er
1	PhMe	rt	70	6:1	74:26
2	CH_2Cl_2	rt	42	2:1	55.5 : 44.5
3	$CHCl_3$	rt	43	2:1	52.5 : 47.5
4	Et_2O	rt	53	3:1	61:39
5	THF	rt	77	10:1	93:7
6	THF	4 °C	79	14:1	95.5 : 4.5
7[b]	THF	4 °C	91	1.3:1	91:9
8	**THF**	**-10 °C**	**75**[c]	**16:1**	**97.5 : 2.5**

[a] All reactions were performed on 0.1 mmol scale at 0.33 M for 12 hours. Yields are NMR yields relative to 1,3,5-trimethoxybenzene as an internal standard; dr determined by crude ^{1}H NMR, er determined by chiral HPLC. [b] With 3 Å MS. [c] Isolated yield.

With optimized conditions (Table 1, entry 8) in hand, we set out to evaluate the scope of chromones that would participate in this transformation (Scheme 3). A 6-nitro substituent did not significantly impact yield or selectivity (**4ba**), and while 6-fluoro substitution led to reduced diastereoselectivity, good yield and enantioselectivity were retained (**4ca**). Other halogen substituents were well-tolerated, and excellent results were observed with both 6-chlorochromone (**4da**) and 6-bromochromone (**4ea**). Recrystallization of the latter upgraded the er to >99.5 : 0.5 and allowed us to determine the absolute and relative stereochemistry of **4ea** – and by analogy, all other products **4** – by x-ray crystallography.

Scheme 3. Scope of Chromone Electrophiles.[a]



[a] All reactions performed overnight on 0.20 mmol scale. Yields are isolated yields; dr determined by crude ^{1}H NMR, er determined by chiral HPLC. [b] Reaction run at 4 °C.

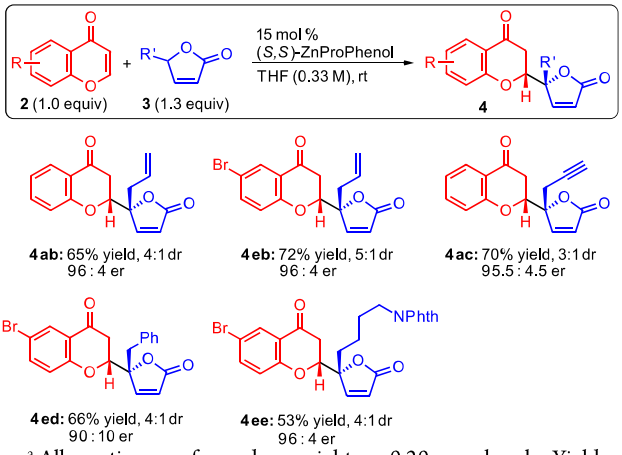
Chromones with electron-donating substituents at the 6-position were particularly good electrophiles. With 6-methylchromone, chromanone lactone **4fa** formed in 93% yield, 5:1 dr, and 92:8 er and with 6-methoxychromone, Michael adduct **4ga** was obtained in near-quantitative yield with 7:1 dr and 98:2 er. Interestingly, shifting the electron-donating substituent to the 7-position resulted in decreased reactivity, though diastereo- and enantioselectivity were unaffected. With 7-methylchromone, partial conversion was observed and **4ha** was obtained in 54% yield with excellent dr and er. Similarly, 7-methoxychomone also partially reacted to afford **4ia** in 49% yield (78% brsm), 6:1 dr, and 95:5 er. Introduction of a second methoxy group at the 5-position was also tolerated and while the reaction stopped at 65% conversion – presumably due to the poor solubility of **2j** – adduct **4ja** was obtained as a single diastereomer in 58% yield with 96.5 : 3.5 er. Finally, we were pleased to find that our method was not limited to chromones. Using thiochromone as the electrophile led to the formation of **4ka** in 76% yield as a single diastereo- and enantiomer. Excellent enantioselectivity was also observed when an *N*-Cbz quinolone was used as the Michael acceptor and although the reaction was sluggish, **4la** was still obtained in 31% yield (61% brsm).

After establishing the electrophile scope, we next set out to see what types of butenolides would participate in this transformation. Due to the ease of synthesis of α,β-butenolides relative to the corresponding

β,γ-unsaturated compounds, we were particularly interested in utilizing the former. While α,β-butenolides did react under the conditions developed for α-angelica lactone **3a**, reactions were sluggish and incomplete conversion was typically observed, presumably due to a kinetically more challenging enolization. Fortunately, this barrier could be overcome by increasing the catalyst loading and reaction temperature, which offered improved yields without substantially impacting diastereo- and enantioselectivity.

To this end, allyl-substituted butenolide **3b** reacted with both chromone and 6-bromochromone to generate the corresponding Michael adducts **4ab** and **4eb** respectively with good yield and diastereoselectivity and 96:4 er (Scheme 4). Similarly, propargyl- (**3c**) and benzyl-substituted butenolides (**3d**) were also suitable substrates. With the former, **4ac** was obtained in 3:1 dr and 95.5 : 4.5 er and with the latter, **4ed** was isolated in 90:10 er with comparable yield and diastereoselectivity. Lastly, a butenolide with a phthalimide on the side chain (**3e**) was also tolerated, and **4ee** was isolated in 53% yield, 4:1 dr, and 96:4 er. While our method is well-suited for 5-substituted butenolides, low conversion was always observed with unsubstituted butenolides.

Scheme 4. Scope of Butenolide Nucleophiles.[a]

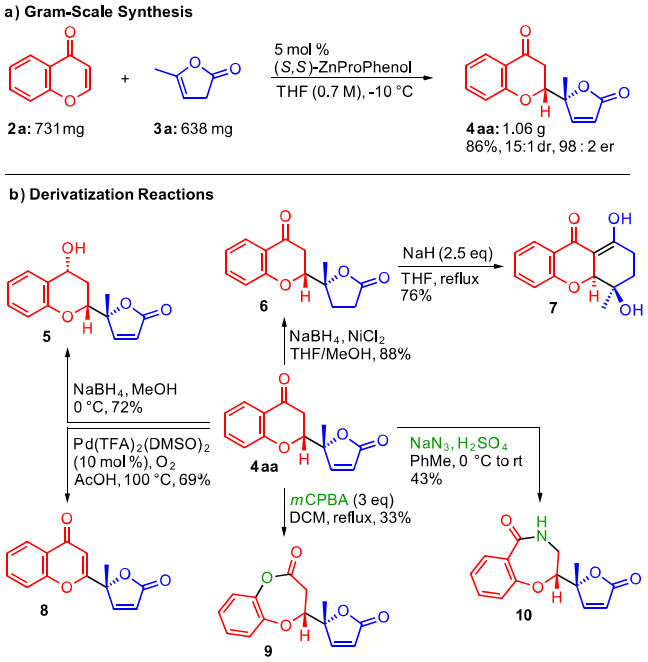


[a] All reactions performed overnight on 0.20 mmol scale. Yields are isolated yields; dr determined by crude ^{1}H NMR, er determined by chiral HPLC.

To demonstrate the scalability of our method, chromanone lactone **4aa** was prepared on gram-scale (Scheme 5). Notably, the reaction could be performed at reduced catalyst loading with no deterioration in yield or selectivity (cf. Scheme 3), and **4aa** was obtained in 86% yield, 15:1 dr, and 98:2 er. With this material in hand, we set out to highlight the synthetic utility of the Michael adducts accessible using our methodology. Reduction of **4aa** with $NaBH_4$ was completely diastereoselective and afforded chromanol **5** as a single stereoisomer in 72% yield. Alternatively, $NaBH_4$ in the presence of $NiCl_2$ selectively reduced the butenolide alkene, furnishing saturated lactone **6** in excellent yield. Upon treatment with sodium hydride, lactone **6** underwent Dieckmann condensation to afford tricycle **7**, which is a tertiary alcohol analog of blennolide B. Interestingly, this cyclization occurred with inversion of stereochemistry at the chromanone, presumably via elimination and readdition of the phenolate ion as proposed by Porco.[4a]

Saegusa oxidation[15] of **4aa** afforded chromone **8**, a noteworthy result given the prevalence of chromones in natural products and pharmaceuticals.[16] Baeyer-Villiger oxidation of **4aa** occurred with the expected selectivity and while it was necessary to halt the reaction prior to full conversion to avoid decomposition, seven-membered lactone **9** could be obtained in 40% yield based on recovered starting material. Interestingly, whereas complete selectivity for aryl migration was observed

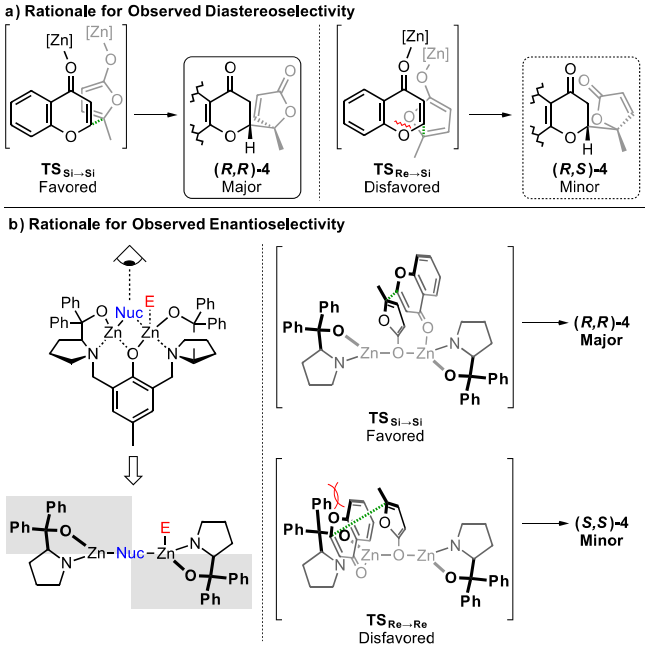
Scheme 5. Gram-Scale Synthesis and Derivatizations.



under Baeyer-Villiger conditions, the opposite was true when **4aa** was treated with hydrazoic acid; the resulting Schmidt rearrangement occurred with complete selectivity for alkyl migration, affording lactam **10** in 43% yield. This curious selectivity has been observed previously for other chromanones.[17]

Since the relative stereochemistry of our products matches that observed by Porco in his work on the addition of siloxyfurans to chromones, we believe that the diastereoselectivity is a feature inherent to this type of transformation. As noted by Porco,[4a] the *Si* → *Si* transition state (Scheme 6, top) bears a remarkable resemblance to an *endo* Diels-Alder transition state, and may thus be stabilized by secondary orbital overlap. On the other hand, the diastereomeric *Re* → *Si* transition state could be destabilized by lone pair-lone pair repulsion

Scheme 6. Proposed Explanation for Selectivity.



between the ring oxygens in the chromone and the butenolide. To explain the observed enantioselectivity, we propose a model based on a crystal structure of the dinuclear Zn-ProPhenol complex bound to a 4-nitrophenolate ion (Scheme 6, bottom).[18] We posit that like the phenoxide, the enolate of the butenolide acts as a bridging ligand between the two zinc centers. The *Si* → *Si* transition state – which leads to the major (*R,R*) product – places the bulk of the chromone in an open quadrant of the catalyst pocket, whereas the enantiomeric *Re* → *Re* transition state generates a steric clash between the chromone and the aryl groups of one of the diphenylprolinol units.

In conclusion, we developed the first asymmetric vinylogous addition of butenolides to chromones. This transformation occurs with good to excellent enantio- and diastereoselectivity and yields are typically high. A variety of substituted chromones – as well as a thiochromone and a protected quinolone – can be used as electrophiles, and both α,β- and β,γ-butenolides function as nucleophiles. Notably, the butenolides participate directly, and preactivation as the siloxyfurans is not necessary. The chromanone lactones accessible using this methodology are versatile scaffolds for further functionalization, and can be rapidly transformed into chromanols, chromones, and tetrahydroxanthones.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, and $^{1}H/^{13}C$ NMR spectra for **4** – **10** and crystallographic data for **4ea** (CCDC 1879288).

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† E. G. and C. A. K. contributed equally.

Notes

The authors declare no competing financial interests.

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