*Allylic Substitution*

# Regio- and Stereoselective Construction of γ-Butenolides through Phosphine-Catalyzed Substitution of Morita–Baylis–Hillman Acetates: An Organocatalytic Allylic Alkylation**

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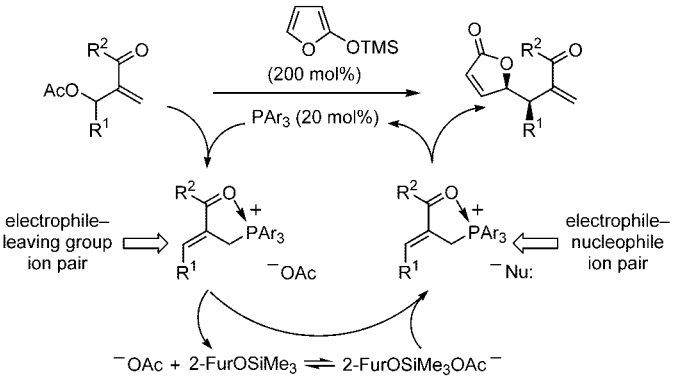
The γ-butenolide ring system ranks among the most ubiquitous structural motifs found in naturally occurring organic molecules.[1] Owing to the prevalence of γ-butenolides, their regio- and stereoselective synthesis has been the focus of intensive effort.[2] In this regard, the use of 2-silyloxy furans as nucleophilic partners in Mukaiyama–aldol-,[3] Mukaiyama–Michael-,[4,5] and Mukaiyama–Mannich-type additions[6] has emerged as an effective strategy. Even broader access to butenolide substructures would be possible through the development of new electrophilic partners amenable to 2-silyloxy furan addition. For example, the use of allylic carboxylates as electrophiles in silyloxy furan addition is unknown and would provide access to γ-butenolides with vicinal stereogenic centers. Herein we disclose that upon exposure of Morita–Baylis–Hillman (MBH) acetates **1a**–**12a** to substoichiometric amounts of triphenylphosphane (20 mol%) in the presence of 2-trimethylsilyloxy furan, regiospecific allylic substitution occurs to provide the products of *C*-allylation, that is, γ-butenolides **1b**–**12b** (Table 1). Good to excellent yields, regioselectivities, and diastereoselectivities are attained and, in the case of the (−)-8-phenylmenthol ester **14a** (Scheme 3), the absolute stereochemical course of the substitution is controlled.

Recently, a two-step protocol for the amination of MBH acetates mediated by DABCO was reported.[7a,b] A related two-step transformation employing quinidine subsequently appeared.[7c] Following reports of these stoichiometric processes, the DABCO-catalyzed decarboxylative rearrangement of MBH carbamates was demonstrated.[7d] Finally, $(DHQD)_2PHAL$ was recently shown to catalyze regioretentive allylic substitution of MBH acetates when using sodium bicarbonate as a nucleophile.[7e] The corresponding MBH alcohols were produced in 25–42% yield with 54–92% *ee*. As part of a program in nucleophilic catalysis based on phosphine conjugate addition,[8] the first *phosphine-catalyzed* allylic substitution of Morita–Baylis–Hillman (MBH) acetates was reported from our lab.[8e] A key feature of this transformation appears to involve the generation of an electrophile–nucleophile ion pair, which suppresses direct addition of the nucleophile to the less substituted enone moiety of the starting MBH acetate. The enone immediately obtained upon addition of the phosphine may also benefit from activation through internal coordination to phosphorus (Scheme 1). In our initial study, an acid–base reaction between the leaving group (acetate) and the pronucleophile (4,5-dichlorophthalimide) served to generate the requisite electrophile–nucleophile ion pair. Given the propensity of organosilicon compounds to form hypervalent anions or "ate" complexes,[9] the development of related catalytic C–C bond formations involving electrophile–nucleophile ion pair intermediates derived from enol silane based pronucleophiles was deemed feasible.




***Scheme 1.*** Postulated catalytic mechanism for γ-butenolide synthesis through tandem $S_N2'$–$S_N2'$ substitution.

To explore this prospect, MBH acetate **1a** (100 mol%) derived from methyl vinyl ketone (MVK) was exposed to 2-trimethylsilyloxy furan (200 mol%) in the presence of triphenylphosphane (20 mol%) in THF solvent (0.3 M) at 0 °C. Gratifyingly, the desired product of allylic substitution, γ-butenolide **1b**, was isolated in 88% yield as a single *syn* diastereomer. The regioisomeric substance **1c** was also formed in 9% yield. Withstanding changes in reaction temperature, these conditions proved general across a range

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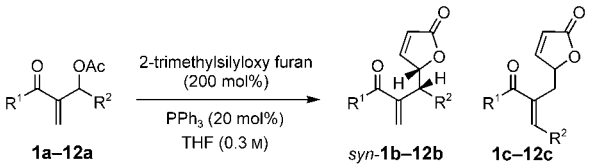
of related MVK-derived MBH acetates **2a**–**6a**, which bear aromatic, aliphatic, cyclopropyl, vinylic, and acetylenic substituents. All MVK-derived products **1b**–**6b** were obtained with diastereomeric ratios of $\geq$20:1 (*syn*/*anti*). Similarly, the corresponding acrylate-derived MBH acetates **7a**–**12a** provide γ-butenolides **7b**–**12b** with excellent regioselectivity. Butenolides **7b**, **8b**, **11b**, and **12b**, which bear aromatic, vinylic, and acetylenic substituents, were obtained with excellent diastereoselectivity. However, acrylate-derived MBH acetates **9b** and **10b**, which bear *n*-alkyl and cyclopropyl substituents, respectively, were obtained with lower diastereoselectivities (Table 1).

The high levels of diastereoselectivity attained in these substitutions do not appear to be consistent with an open transition state. It is possible that the high diastereoselectivity arises as a consequence of a mechanism involving *endo*-selective Diels–Alder cycloaddition of the siloxy furan ate complex with the enone obtained upon the addition of the phosphine followed by subsequent Grob-type fragmentation. Structurally related silyloxy furan-enone [4+2] cycloadducts have been isolated. Notably, the high levels of diastereoselectivity observed in the formation of **1b**–**12b** require that the intermediate phosphine adducts appear as single enone geometrical isomers, irrespective of which mechanism is operative (Scheme 2).[5b]

***Table 1:*** Diastereoselective phosphine catalyzed allylic substitution of MBH acetates to form γ-butenolides.[a,b]




**1a–12a** → *syn*-**1b–12b** + **1c–12c**

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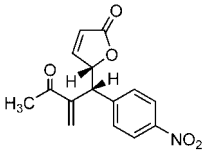
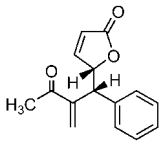
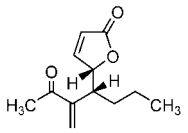
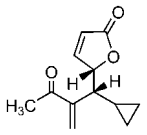
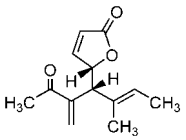
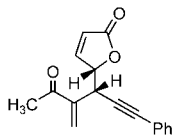
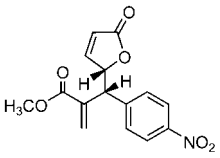
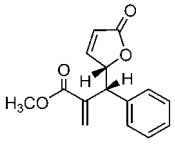
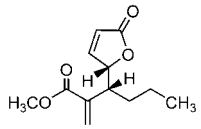
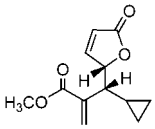
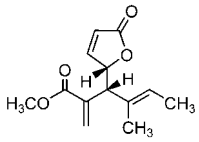
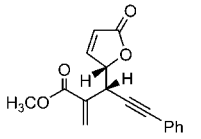
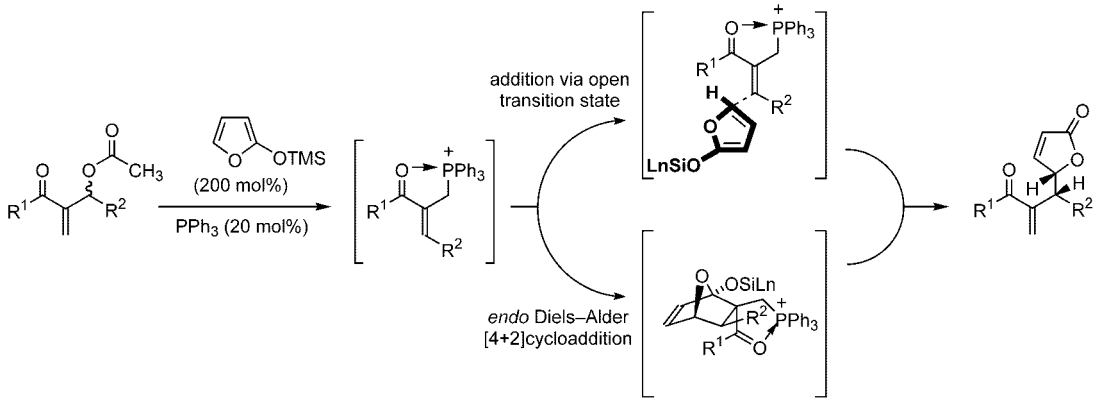
|---|---|---|
|  **1b**, 88%, >95:5 d.r.<br>**1c**, 9% |  **2b**, 80%, >95:5 d.r.<br>**2c**, 5% |  **3b**, 63%, >95:5 d.r.<br>**3c**, 7% |
|  **4b**, 80%, 20:1 d.r.<br>**4c**, 5% |  **5b**, 45%, >95:5 d.r.<br>**5c**, 10% |  **6b**, 88%, 24:1 d.r.<br>**6c**, 5% |
|  **7b**, 84%, >95:5 d.r.<br>**7c**, 6% |  **8b**, 86%, >95:5 d.r.<br>**8c**, 1% |  **9b**, 67%, 2.8:1 d.r.<br>**9c**, not observed |
|  **10b**, 83%, 3.5:1 d.r.<br>**10c**, not observed |  **11b**, 62%, >95:5 d.r.<br>**11c**, not observed |  **12b**, 94%, >95:5 d.r.<br>**12c**, not observed |

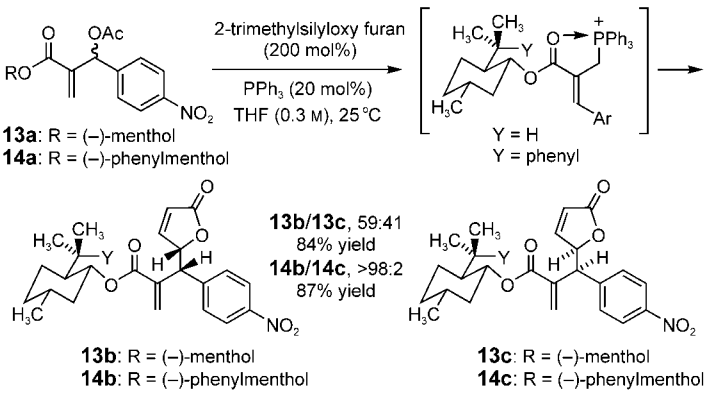
[a] Procedure: THF (1.6 mL, 0.3 M) was added to a reaction vessel charged with the MBH acetate (0.5 mmol, 100 mol%), 2-trimethylsilyloxy furan (1.0 mmol, 200 mol%), and $PPh_3$ (0.1 mmol, 20 mol%). The reaction mixture was allowed to stir at 0°C (**1a**, **6a**, **7a**), 25°C (**2a**, **4a**, **5a**, **8a**, **12a**), 50°C (**3a**), or 80°C (**9a**–**11a**) until complete consumption of starting material was observed, at which point the reaction mixture was adsorbed onto silica gel by evaporation of the solvent, and the product was isolated by silica-gel chromatography. [b] A diastereomeric ratio of >95:5 indicates that the minor isomer could not be detected by $^1$H NMR spectroscopy.




***Scheme 2.*** Alternate mechanisms postulated for the phosphine-catalyzed allylic substitution of MBH acetates to form γ-butenolides.

To control the absolute stereochemical course of this transformation, a chiral auxiliary approach was explored. Whereas (−)-menthol ester **13a** provides the γ-butenolides **13b** and **13c** in good yield, poor levels of asymmetric induction are observed. In contrast, the corresponding (−)-8-phenylmenthol ester **14a** provides the γ-butenolide **14b** in excellent yield and with complete levels of stereocontrol (Scheme 3). The diastereomeric butenolide **14c** was not observed. The stereochemical assignment of **14b**, which is supported by X-ray diffraction analysis, led to the indicated model for stereochemical induction.




***Scheme 3.*** Controlling the absolute stereochemical course of allylic substitution through the use of (−)-8-phenylmenthol ester **14a**.

In summary, upon exposure of MBH acetates **1a**–**12a** to 2-trimethylsilyloxy furan in the presence of substoichiometric quantities of triphenylphosphine, highly regio- and stereoselective substitution occurs to provide γ-butenolides **1b**–**12b**. Moreover, as demonstrated by the substitution of MBH acetate **14a**, the absolute stereochemical course of these transformations is controlled through the use of the (−)-8-phenylmenthol ester. Future studies will focus on the development of related transformations, including enantioselective variants of the transformation described herein.

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**Keywords:** allylic substitution · butenolides · C–C coupling · organocatalysis

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