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Chemoselective Synthesis of Trifluoromethylated γ-Butenolide Derivatives via Phosphine-Promoted Tandem Reaction of Allylic Carbonates and Trifluoromethyl Ketones

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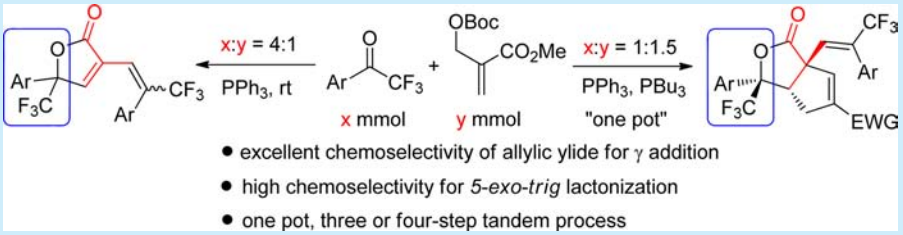
Supporting Information



ABSTRACT: A novel chemoselective phosphine-mediated tandem reaction between nonsubstituted MBH carbonates and aryl trifluoromethyl ketones is described. The product selectivity of the reaction is easily tunable by changing the ratios of the two reactants, and mono- or bicyclic bistrifluoromethylated vinyl γ-butenolide products can be prepared with good chemoselectivity in modest-to-good yields and diastereoselectivities. The formation of the bicyclic γ-butenolide structures via a one-pot four-step sequence under phosphine catalysis is unprecedented.

The γ-butyrolactone is a ubiquitous structural component present in a plethora of naturally occurring compounds (~10% of all natural products),[1] including the famous micronutrient ascorbic acid[1b] and plant growth regulator karrikin.[1c] The fused bicyclic γ-butyrolactone also occurs as characteristic skeletal core in some biointeresting natural products[2] (Figure 1),

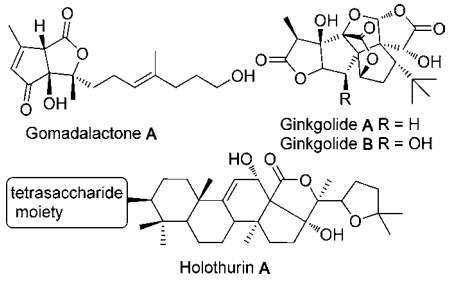


Figure 1. Representative natural compounds with fused bicyclic γ-butyrolactone.

such as gomadalactone **A**, the contact sex pheromone component of white-spotted longicorn beetles;[2b] holothurin **A**, the triterpene glycoside occurring as secondary metabolites in sea cucumbers;[2c] and ginkgolides **A** and **B**, the medicinally useful trilactones isolated from the Ginkgo tree leaves.[2d] There have been a growing number of reports on the synthetic protocols for construction of the γ-butyrolactone structure.[3] Further, trifluoromethylated analogs of bioactive molecules frequently exhibit unique physical, chemical, and physiological properties for broad applications in various fields including chemical biology and drug discovery.[4] However, efficient and step-economical approaches to trifluoromethylated analogs of γ-butenolides and fused [4.4] oxobicycle structures from readily accessible reagents and starting materials remain very limited.

Recently, nucleophilic phosphine organocatalysis has evolved into a powerful strategy to access various synthetically valuable small-ring carbon- and heterocycles.[5,6] Besides allenes and alkynes, MBH (Morita−Baylis−Hillman) adducts have also become common coupling partners in this system since the pioneering work of Lu in 2003.[7] The zwitterion generated from the nucleophilic addition of a phosphine to an MBH adduct shows diverse reactivities in a range of reactions, with α- or γ-selectivity being a particularly challenging issue. For aromatic aldehyde-derived MBH carbonates (γ-substituted), the preference for α- or γ-attack often depends on the nature of the electrophilic coupling partner employed.[8] As the simplest MBH carbonate, the formaldehyde-derived MBH carbonates (γ-nonsubstituted) usually favor γ-attack due to steric encumbrance from the adjacent phosphonium group in the α-attack, and thus these are among the most studied MBH carbonates with various coupling partners.[9] In addition, this type of MBH carbonates are also highly reactive for the development of a tandem process.[8a,10] Despite these advances, simple aldehydes and ketones have

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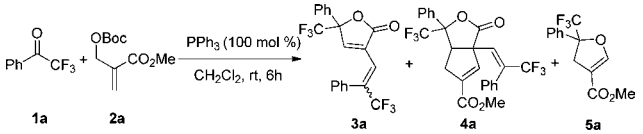
seldom been employed in phosphine-catalyzed tandem annulations, which may be ascribed to the high propensity of their carbonyl group to undergo direct Wittig olefination.[8b,c] We disclose herein a novel tandem reaction between formaldehyde-derived MBH carbonates and aryl trifluoromethyl ketones.[11] With this method, two sets of bistrifluoromethylated vinyl γ-butenolide derivatives bearing mono- or bicyclic skeletons have been synthesized with good chemoselectivity.

Initially, when a solution of equimolar amounts of phenyl trifluoromethyl ketone **1a**, allylic carbonate **2a**, and PPh_3 in CH_2Cl_2 was stirred for 6 h at rt, three identifiable products **3a** (*E*/*Z* = 6:1, inseparable mixture), (*E*)-**4a**, and **5a** were isolated with poor chemoselectivity (Scheme 1). The structures of **3a** and (*E*)-**4a** were unambiguously confirmed by X-ray crystallographic analysis.[12] As expected, all three compounds resulted from γ-addition of the allylic phosphonium ylide generated *in situ* from **2a** and PPh_3 to the ketone carbonyl, and no direct Wittig olefination product was detected. Conceivably, the formation of γ-butenolide **3a** could be easily explained by a tandem lactonizaton[13]/Wittig[14] sequence, and since **3a** is electron-deficient it can further undergo [3 + 2] cycloaddition with another molecule of **2a** to provide bicyclic γ-butenolide(*E*)-**4a** as a single diastereomer.[15] The dihydrofuran **5a** was produced by direct P-catalyzed [3 + 2] cycloaddition of **2a** and **1a**, which was similar to the reaction of nonsubstituted allenoates with CF_3 ketone.[6f] Increasing the amount of the ketone **1a** was found to improve the chemoselectivity of the reaction, and the use of 4 equiv of **1a** led to an 82% isolated yield of γ-butenolide **3a**. However, varying other reaction conditions such as solvent, temperature, and phosphine promoters with different electronic properties all failed to improve the yield of **3a** further.[16]

Scheme 1. Optimization of Substrate Ratio for Chemoselective Synthesis of Lactone 3a

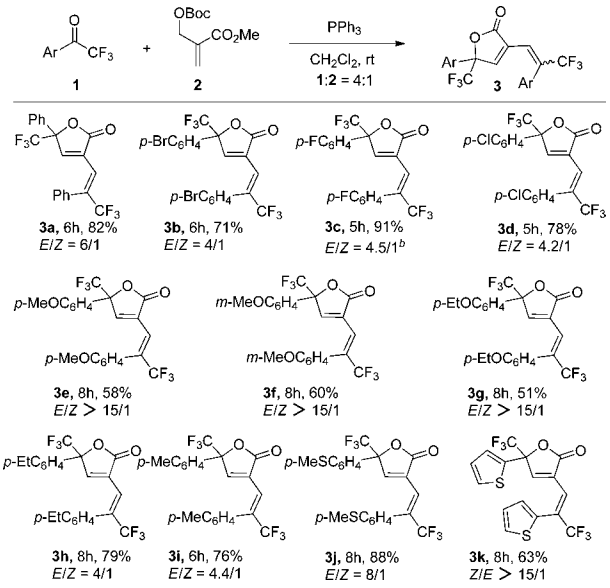


Having identified the optimal conditions for the chemoselective formation of γ-butenolide **3a**, the scope of the tandem vinylogous addition/lactonization/Wittig reaction sequence was examined with different aryl trifluoromethyl ketones (Scheme 2). In general, a range of vinyl γ-butenolides containing a CF_3-substituted quaternary stereogenic center were conveniently prepared in moderate-to-good yields and *E*/*Z* selectivities. The electronic nature of the substituents on the aryl groups of ketone **1** had a dramatic influence on both the yield and *E*/*Z* selectivity of the reaction: ketones with electron-withdrawing and -neutral substituents usually gave higher chemical yields but moderate *E*/*Z* selectivity, while those with electron-donating substituents provided modest yields but good *E*/*Z* selectivity.[17] Notably, the heteroaryl substrate **1k** was also tolerated in the tandem reaction system with similar reactivity to substrates with electron-donating substituents. However, the aliphatic ketone, α,α,α-trifluoroacetone, hardly reacted under the typical reaction conditions.

Next, we set out to optimize the reaction conditions for the chemoselective synthesis of the bicyclic lactone products **4**. After some experimentation, we developed a one-pot protocol involving sequential vinylogous addition/lactonization/Wittig/cycloaddition for this: the reaction was first conducted with a ketone/carbonate ratio of 2:1 in the presence of 100 mol % of PPh_3 for 6 h to produce lactone **3a** as the predominant product. Then two more equivalents of the MBH adduct carbonate **2a** and PBu_3 (100 mol %)[18] were added to the reaction mixture to furnish bicyclic γ-butenolide (*E*)-**4a** in 70% isolated yield, together with (*Z*)-**4a** in 8% yield[19] and the dihydrofuran **5a** in 5% yield (Scheme 3). It is worth mentioning that up to five new chemical bonds including four new C−C bonds, two adjacent quaternary centers, and one tertiary stereogenic center were created under very mild conditions in this one-pot four-step transformation. A subsequent substrate scope study proved that the reaction was general only for aryl trifluoromethylketones (Scheme 3). Regardless of the electronic nature of the substituents on the aryl group of the ketone, the desired fused[4.4]bicyclic γ-butenolides **4** were obtained in acceptable yields and with generally excellent diastereoselectivities (dr> 15:1). In most cases, high *E*/*Z* selectivity favoring the formation of (*E*)-**4a** and good chemoselectivity were also observed. One exception is the heteroaromatic 2-thienyl trifluoromethyl ketone **1k**, in which exclusive (*E*)-selectivity was observed, albeit with the formation of a considerable amount of compound **5k**. In addition, three other MBH adducts were also investigated as the coupling partner instead of **2a** (in second batch). It was found that either increasing the steric hindrance around the ester group or replacing it with a ketone group would lead to inferior results.

To gain insight into the mechanism of the tandem reaction, two control experiments were carried out (Scheme 4). Notably, the use of aryl trifluoromethyl ketones **1** in this reaction is privileged. In this regard, they not only enable ready access to useful CF_3-containing compounds but also are crucial for good

Scheme 2. Tandem Vinylogous Addition/Lactonization/Wittig Reactions of Aryl Trifluoromethyl Ketones 1 with Allylic Carbonate 2[a]



[a]Unless otherwise noted, all reactions were carried out with **1** (0.2 mmol) and **2** (0.05 mmol) in the presence of PPh_3(0.05 mmol) in CH_2Cl_2 (1.0 mL) for 5−8 h at rt; isolated yields of **3** as inseparable *E*/*Z* mixture; *E*/*Z* ratios were determined by ^1H NMR analysis. [b] The *E* and *Z* isomers of **3c** could be separated by preparative TLC.

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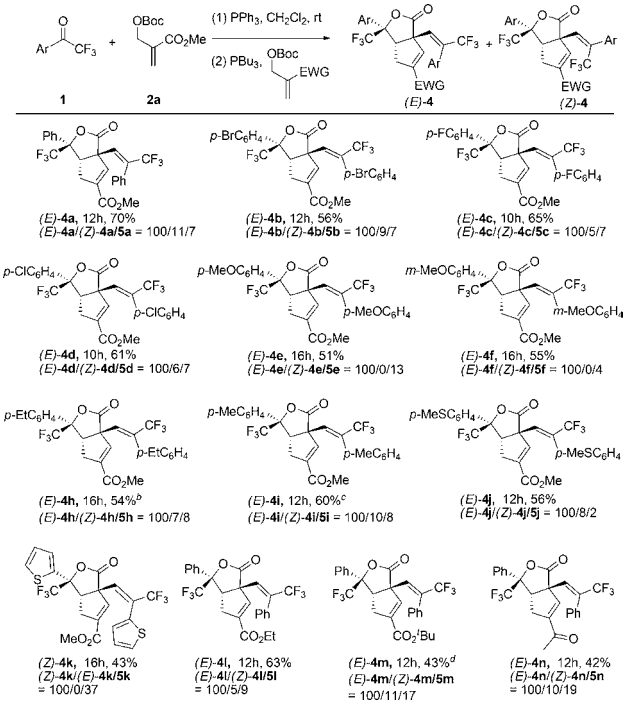
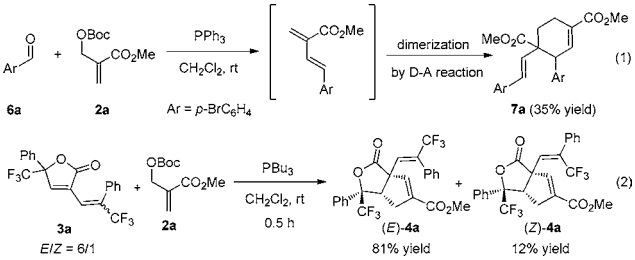
Scheme 3. Tandem Vinylogous Addition/Lactonization/Wittig/Cycloaddition Reactions of Aryl CF_3 Ketones 1 with Allylic Carbonate 2[a]



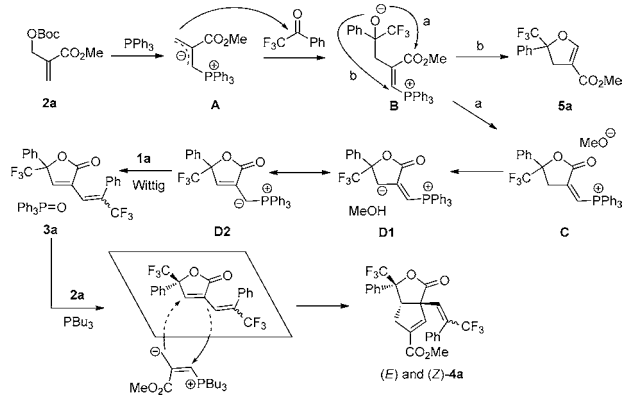
[a]Unless otherwise noted, all reactions were carried out with **1** (0.1 mmol) and **2a** (0.05 mmol) in the presence of PPh_3 (0.05 mmol) in CH_2Cl_2 (1.0 mL) for 5−8 h at rt, and then **2** (0.1 mmol) and PBu_3 (0.1 mmol) were added; the resultant mixture was stirred for another 5−8 h; yields of isolated (*E*)-**4** provided; ratios were calculated based on the isolated yields of each compound. [b] Lactone **3h** was also isolated in 5% yield (*E*/*Z* = 1.4:1). [c] Lactone **3i** was also isolated in 5% yield (*E*/*Z* = 1:2). [d] The dr of (*E*)-**4m** was 9/1; other bicycles(*E*)-**4** were isolated generally with >15/1 dr.

Scheme 4. Two Control Experiments



chemoselectivity. When *p*-bromophenylaldehyde **6a** was used in lieu of **1a** under similar reaction conditions, only product **7a** derived from direct Wittig olefination was isolated as the sole product albeit with a poor yield (Scheme 4, eq 1).[20] The bulky CF_3 group in **1** might be responsible for the absence of this type of product in our system for it might favor the γ-addition of the zwitterion A (see Scheme 5) to minimize steric repulsion from the phosphonium group.[9b] Moreover, the control experiment between isolated γ-butenolide **3a** and MBH carbonate **2a** proceeded swiftly to produce **4a** in high yield with *E*/*Z* selectivity similar to that observed in the one-pot procedure, thus verifying the intermediacy of **3a** in the formation of **4a** (Scheme 4, eq 2). Further treatment of **4a** with MBH carbonate under the otherwise identical conditions proved fruitless.

Scheme 5. A Plausible Reaction Mechanism



Based on the above observations and previous reports, a plausible reaction mechanism is outlined as shown in Scheme 5. Initially, the MBH carbonate **2a** is converted to γ-nonsubstituted allylic phosphorus ylide **A** via a well-defined S_N2' addition/deprotonation process with the nucleophilic phosphine. The zwitterion **A** then undergoes exclusive γ-addition to the ketone **1** to produce betaine **B**. There are two competitive pathways for the ensuing annulation of **B**. The first one is 5-*exo*-*trig* lactonization to provide intermediate **C**. The other one is a 5-*endo*-*trig* process leading to the formation of dihydrofuran **5a**.The first one leading to the product **3a** is favored according to Baldwin's rules. Intermediate **C** may be deprotonated by the *in situ* generated methoxide anion to form zwitterion **D1**/**D2**. Subsequently, **D2** can undergo Wittig olefination with the CF_3 ketone **1a** to give product **3a**. We presume that the irreversibility of the Wittig olefination, which might be more facilitated by the presence of a large excess of ketone **1**, should also be one of the key factors determining the chemoselectivity.[21] Finally, the vinyl γ-butenolide **3a** can function as an electrophilic alkene partner to undergo a traditional phosphine catalyzed [3 + 2] cycloaddition with another molecule of MBH carbonate **2a**. The high diastereoselectivity observed in the cycloaddition step can be roughly explained by the postulated model: to fulfill the donation of an oxygen lone pair to the adjacent C−CF_3 σ^* orbital, the strongly electronegative CF_3 group takes a pseudoaxial orientation,[22] and then the zwitterion may approach the conjugate α,β-unsaturated double bond of **3a** preferentially from the face opposite to the axial CF_3 group.

In summary, we have developed a novel chemoselective phosphine-mediated tandem reaction between nonsubstituted MBH carbonates and aryl trifluoromethyl ketones, which provides facile access to bistrifluoromethylated vinyl γ-butenolides and bicyclic γ-butenolides with three contiguously adjacent stereogenic centers under mild reaction conditions. With simple manipulations of the reaction conditions, such as altering the ratios of the two starting materials, adding the MBH carbonate in batches together with an additional phosphine mediator, the two types of products could be obtained in moderate-to-good yield, with high chemo- and stereoselectivity. The new chemistry affords a step-economical approach to CF_3-substituted scaffolds with structural complexity from readily available starting materials and adds to the arsenal of nucleophilic organophosphine catalysis.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and X-ray structures of **3a** and (*E*)-**4a** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) CCDC 1019156 (**3a**) and 1019155 ((*E*)-**4a**) contain the crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(16) The use of Bu_3P improves the product *E*/*Z* ratio in the Wittig olefination with arylaldehyde-derived MBH carbonates and CF_3 ketone; see ref 8b. However, this did not work in our case.

(17) For the substituent effect of the carbonyl compound on the *E*/*Z* selectivity of Wittig olefination, see: (a) Stępień, M. *J. Org. Chem.* **2013**, *78*, 9512. (b) Takeuchi, K.; Paschal, J. W.; Loncharich, R. J. *J. Org. Chem.* **1995**, *60*, 156.

(18) The use of 0.5 equiv of Bu_3P in the second batch would cause a visible drop in the yield of **4a** (57% yield), though a stoichiometric amount of phosphine was unnecessary for [3 + 2] cycloaddition theoretically.

(19) Noteworthy was that the yield of (*Z*)-**4a** was not consistent with the aforementioned *E*/*Z* ratio in **3a**, which would be partly attributed to the different reactivity of *E* and *Z* isomers of **3** in [3 + 2] cycloaddition. The ^{1}H NMR analysis of some recovered **3** (**3h** and **3i**) samples indicated a dramatically changed *E*/*Z* ratio.

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(21) The steric hindrance of the ester groups in the MBH carbonates **2** also showed an influence on the chemoselectivity: when the methyl group of MBH carbonate was replaced with a bulky group such as *tert*-butyl, the lactonization step was disturbed and the formation of 5-*endo*-*trig* product **5** increased; see Supporting Information for details.

(22) For the pseudoaxial orientation of the CF_3 group in the crystal structure of (*E*)-**4a**, see Supporting Information. We thank one of our reviewers for proposing this rationale.

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