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A Copper(I)-Catalyzed Addition/Annulation Sequence for the Two-Component Synthesis of γ-Ylidenebutenolides

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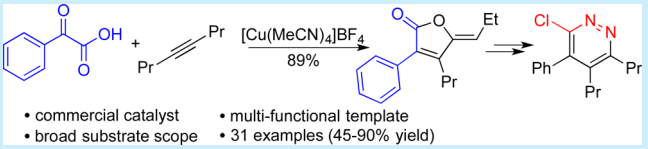
Supporting Information

ABSTRACT: A highly efficient Cu(I)-catalyzed addition/annulation sequence has been developed for the synthesis of (*Z*)-ylidenebutenolides employing readily available α-ketoacids and alkynes as substrates. The reactions employ a simple commercially available Cu(I)-catalyst, display good substrate scope, and deliver products with high stereoselectivity. The synthetic utility of the method is demonstrated by the straightforward derivatization of the ylidenebutenolides into a diverse range of heterocycles, and also by the preparation of the natural product bovolide, and analogs thereof.

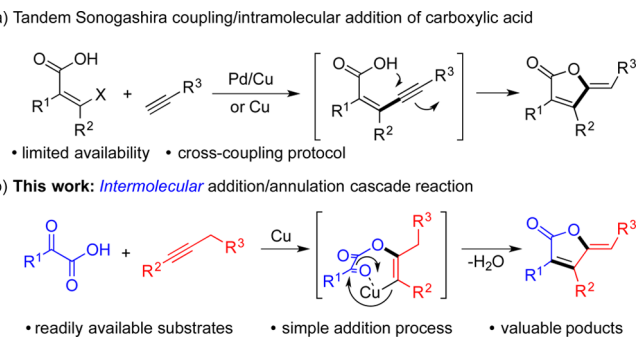


Butenolides are important motifs present in many thousands of natural products and are responsible for a diverse range of biological activities.[1] They also feature as valuable intermediates for the synthesis of related heterocycles and natural products.[2] A consequence of these attributes is that the development of synthetic methods for the construction of such building blocks has attracted much attention.[3,4] However, the synthesis of γ-ylidenebutenolides, a class of butenolides that features synthetically useful *exo*-alkene functionalities, is significantly less developed.[3a,d,e,5]

Classical methods to prepare γ-ylidenebutenolides rely on the modification of pre-existing oxygen-containing five-membered heterocycles, such as maleic anhydrides (Wittig or Wadsworth–Emmons olefination),[6] 2-oxyfurans (aldol condensation),[7] and γ-lactones (Wittig or aldol condensation).[8] While these protocols still represent some of the most widely used methods, they are often nonselective and low-yielding, and the stepwise synthesis of the starting heterocyclic framework is often required.

Simple addition processes represent almost ideal reactions for synthesis,[9] delivering value-added products with complete atom economy.[10] Hydrocarboxylation reactions, based on the combination of carboxylic acids with alkenes or alkynes, are important examples of this class of reaction that lead to synthetically useful products.[11] Intramolecular reactions of this type have been reported for the synthesis of γ-ylidenebutenolides,[12] and high levels of regio- and stereoselectivity can be achieved using transition metal catalysis.[13] For example, the Pd- or Cu-catalyzed lactonization of *in situ* generated 2-en-4-ynoic acids proceed via a 5-*exo*-dig cyclization and generate the γ-ylidene functionality through intramolecular hydrocarboxylation (Scheme 1a).[14] However, despite the improvements that have been achieved, these reactions still suffer from poor availability of starting materials, the preparation of which can be challenging, and this in turn limits the substitution patterns that are accessible in the products. In particular, reactions that provide a wide range of substituents at both α- and β-positions are rare.[15]

Scheme 1. Intra- and Intermolecular Addition of Carboxylic Acids to Alkynes for the Synthesis of γ-Ylidenebutenolides



We wanted to develop an alternative method for γ-ylidenebutenolide synthesis employing simple and more readily available starting materials, and envisioned that the intermolecular addition of α-ketoacids to alkynes should provide useful intermediates for the cyclization to the desired butenolide products (Scheme 1b). The attractive, sustainable chemistry profile of intermolecular addition processes is often compromised by the need to employ precious-metal catalysts, with ruthenium- and rhodium-based systems, often the metals of choice. Here, we report that simple copper(I) complexes can catalyze the addition/annulation cascade reaction for the synthesis of γ-ylidenebutenolides.[16]

We chose commercially available 2-oxo-2-phenylacetic acid and 1-octyne **1a** for optimization studies (Table 1) and initially focused on identifying a suitable catalyst, with lead reactions conducted using toluene as solvent at 130 °C. No desired product was observed using the precious metal catalysts commonly employed in related reactions, with Rh complexes leading to only hydrocarboxylation adducts, and Au systems

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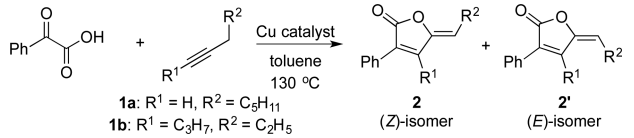
Table 1. Optimization of Reaction between 2-Oxo-2-phenylacetic Acid and Octynes[a]



entry	alkyne	catalyst (equiv)	yield **2** (%)	yield **2′** (%)
1	**1a**	Cu_2O (1.0)	44	19
2	**1a**	Cu(3-Me-Sal) (1.0)	53	10
3	**1a**	Cu(3-Me-Sal) (0.2)	44	11
4[b]	**1a**	Cu(3-Me-Sal) (0.2)	5	2
5	**1a**	$[Cu(MeCN)_4]BF_4$ (0.2)	74	16
6[c]	**1a**	$[Cu(MeCN)_4]BF_4$ (0.1)	80(76)[d]	19(19)[d]
7[c]	**1b**	$[Cu(MeCN)_4]BF_4$ (0.1)	50	0
8[c]	**1b**	$[Cu(MeCN)_4]BF_4$ (0.2)	96	0
9[c,e]	**1b**	$[Cu(MeCN)_4]BF_4$ (0.1)	95(89)[d]	0

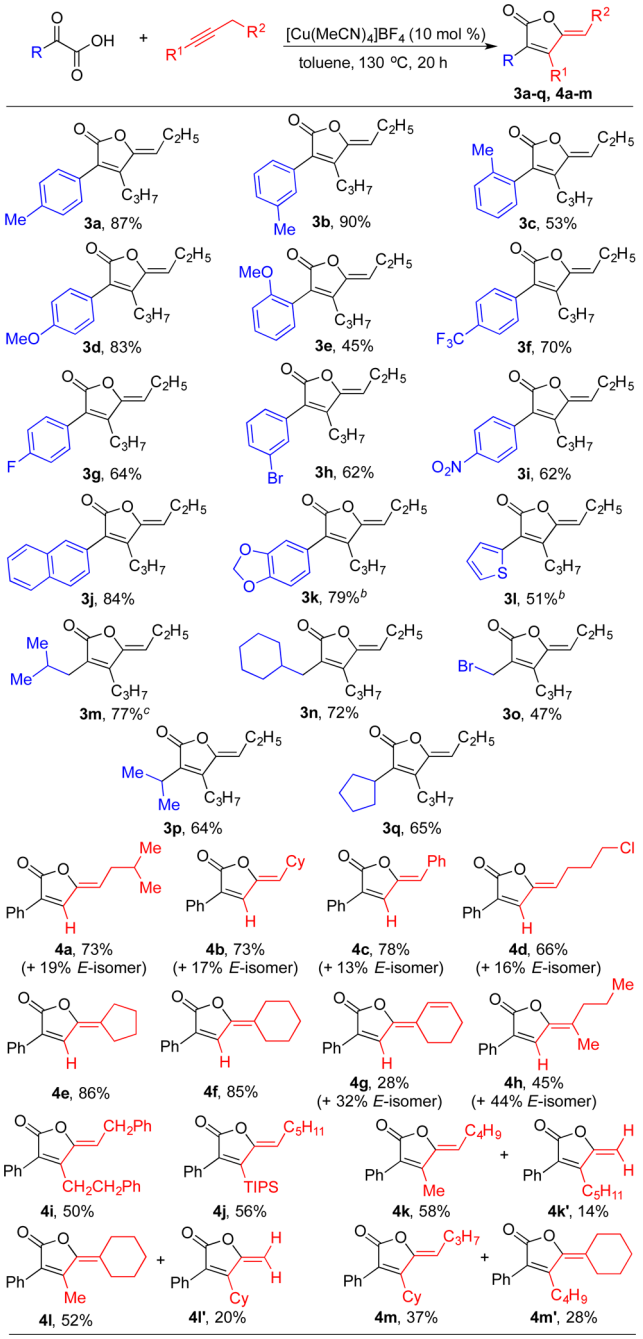
[a]Reaction conditions: 2-Oxo-2-phenylacetic acid (0.3 mmol), octynes (0.6 mmol), catalyst (as stated), toluene (1.5 mL), 130 °C, 20 h; Cu(3-Me-Sal) = copper(I) 3-methylsalicylate. Yields determined by ^1H NMR of crude mixtures using nitromethane as an internal standard. [b]Reaction under air. [c]2-Oxo-2-phenylacetic acid (0.36 mmol) and octynes (0.3 mmol). [d]Isolated yields. [e]0.3 mL of toluene.

showing no reactivity. Zn- and Ag-based catalysts were also found to be ineffective (see Supporting Information for full details). Pleasingly, the use of Cu_2O in stoichiometric amounts afforded the desired products in moderate yields (entry 1), with the thermodynamically favored (*Z*)-isomer formed as the major product. Other Cu(I) sources, such as Cu(I) 3-methylsalicylate (Cu(3-Me-Sal)), were also efficient (entry 2), and crucially, a reaction employing substoichiometric amounts of catalyst proved effective (entry 3). The use of an air atmosphere dramatically reduced the yield (entry 4), indicating that a Cu(II) species was unlikely. Full conversion was obtained by switching to $[Cu(MeCN)_4]BF_4$ (entry 5), and further optimization revealed that the catalyst loading could be reduced to 10 mol % using the alkyne as the limiting reagent (entry 6). The reactivity of an internal alkyne **1b** was then evaluated (entry 7), and excellent yields could be achieved by either increasing the catalyst loading (entry 8) or performing the reaction in more concentrated solutions (entry 9). Importantly, the introduction of a β-substituent in the products enhanced the stereoselectivity of the reactions and exclusively generated the (*Z*)-isomer **2b**.

With the optimal conditions in place, we explored the scope of α-ketoacids in combination with 4-octyne (Scheme 2). Methyl substituents could be placed at all positions of the phenyl ring (**3a–c**), and both electron-rich (**3d** and **3e**) and electron-poor (**3f–3i**) aryl substrates were well tolerated. Halogen-substituted arenes were compatible with the reaction conditions (**3g** and **3h**), as were 2-naphthyl (**3j**) and heterocyclic substrates (**3k** and **3l**). The scope was not limited to aryl substrates, with a variety of alkyl ketoacids also affording the butenolide products in good yields (**3m–3q**). An alkyl bromide substituent could be introduced (**3o**), thus providing a functional handle for installing diverse functional groups. Finally, substrates featuring hindered alkyl substituents were also effective (**3p** and **3q**).

We next investigated the alkyne substrate scope. A linear aliphatic alkyne (**4a**) and cyclohexyl-substituted alkyne (**4b**) performed well, while a benzyl alkyne (**4c**) resulted in the

Scheme 2. Substrate Scope in Cu(I)-Catalyzed γ-Ylidenebutenolide Synthesis[a]



[a]Reaction conditions: Alkyne (0.3 mmol), α-ketoacid (0.36 mmol), $[Cu(MeCN)_4]BF_4$ (0.03 mmol), toluene (0.3 mL or 1.5 mL), 130 °C, 20 h. [b]1,1,2-Trichloroethane was used as solvent. [c]2 equiv of α-ketoacid was used.

arylidene products in good yields with improved selectivity. A primary alkyl chloride substituent was tolerated (**4d**), providing another example of the good functional group compatibility of the process. Carbocyclic alkynes were excellent substrates (**4e** and **4f**), providing single products in high yields. An alkenyl-substituted alkyne afforded synthetically interesting trienyl products in a 60% combined yield (**4g**); however, poor stereoselectivity was obtained (*Z*/*E* = 1:1). Likewise, a branched aliphatic alkyne gave (*Z*)- and (*E*)-products in a 1:1

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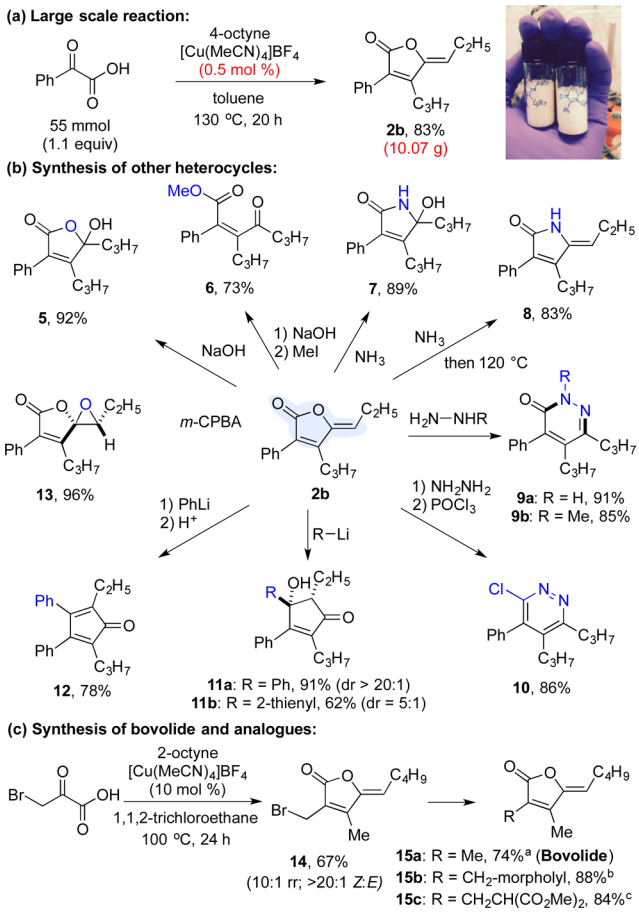
ratio in good yields (**4h**). A symmetrical internal alkyne gave the corresponding product as a single isomer (**4i**). A silyl-substituted alkyne could also be employed and delivered a single alkene isomer as the product (**4j**). Methyl-substituted unsymmetrical alkynes delivered regioisomeric products in good yields with modest selectivity (**4k**/**4k′** and **4l**/**4l′**), while only minimal selectivity was observed when an *n*-butyl/cyclohexyl substituted alkyne was employed (**4m**/**4m′**).

We performed large-scale reactions using 2-oxo-2-phenylacetic acid and 4-octyne as substrates (Scheme 3a). Pleasingly,

Scheme 3. (a) Large Scale Reaction between 2-Oxo-phenylacetic Acid and 4-Octyne, (b) Derivatization of 2b to Other Heterocycles, and (c) Synthesis of Bovolide and Its Analogs

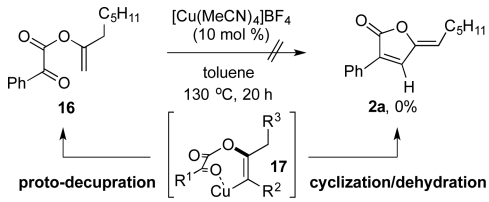


[a]Zn, NH_4Cl (aq). [b]Morpholine, Na_2CO_3. [c]Dimethyl malonate, NaH.

the reaction could be carried out on a 50 mmol scale, producing 10 g of product **2b** using only 0.5 mol % of the Cu(I) catalyst. The product was purified by a simple filtration through silica gel, followed by recrystallization, thus avoiding the need for column purification. γ-Ylidenebutenolides such as **2b** feature a variety of functional groups, with ester, enoate, and enol ester groups present, and can be converted into a range of alternative structures using a series of selective transformations (Scheme 3b). For example, hydrolysis of lactone **2b** with NaOH provides γ-hydroxybutenolide **5**. Treatment of the acid with methyl iodide allowed isolation of γ-keto ester **6**.[4e] Reaction of lactone **2b** with ammonia afforded γ-hydroxypyrrolone **7**, or γ-ylidenepyrrolone **8** if heating was employed. Pyridazinones **9a** and **9b** were obtained when **2b** was reacted with the relevant hydrazines, and subsequent treatment of **9a** with phosphoryl trichloride produced chloro-pyridazine **10**.[17] The cascade organolithium substitution/intramolecular aldol reactions of **2b** gave the cyclopentenone products **11a** and **11b** in good yields and high diastereoselectivities. Subsequent treatment of cyclopentenone **11a** with acid resulted in dehydration and delivered cyclopentadienone **12**.[18] Finally, treatment with *m*-CPBA regioselectively generated the epoxide **13** in excellent yield. This demonstration of the varied reactivity available in γ-ylidenebutenolide products augurs well for their utility as multifunctional templates in discovery chemistry programs. In addition to possible applications to the preparation of designed structures, γ-ylidenebutenolides also provide opportunities to access several natural product topologies. We investigated application of the developed chemistry to the synthesis of the simple natural product bovolide[19,20] and its derivatives (Scheme 3c). The reaction of pyruvic acid with 2-octyne was found to be ineffective, providing **15a** in a disappointing 8% yield. A more reactive, commercially available bromo-substituted acid was employed instead, which delivered the corresponding butenolide **14** in 67% yield. Reductive debromination[21] of **14** using Zn then provided bovolide **15a**. In addition, simple substitution reactions of **14** allowed the access to α-substituents that were not accessible directly, affording the analogs **15b** and **15c** in good yields.

Finally, the formation of the hydrocarboxylation product **16** was observed in several of the copper-catalyzed reactions we explored during our optimization studies, and we speculated whether this was an intermediate involved in a stepwise process toward ylidenebutenolides. However, the butenolide product **2a** was not obtained when **16** was treated under the optimized reaction conditions (Scheme 4), suggesting that the alkenyl-Cu

Scheme 4. Investigation into the Intermediacy of Enolester 16



intermediate **17** directly undergoes intramolecular nucleophilic addition, followed by dehydration to afford **2a**, while **16** is formed via irreversible proto-decupration. The coordination of Cu to the α-keto functionality is believed to play a role in favoring the cyclization process. Interestingly, the proto-decupration pathway is favored when 1,1,1-trifluorononon-2-yne is used as the alkyne component, resulting in the hydrocarboxylation product as the major product (see Supporting Information for details). Further mechanistic studies are under investigation.

In conclusion, we have developed a Cu(I)-catalyzed addition/annulation reaction between α-ketoacids and alkynes that provides a wide range of α- and β-substituted (*Z*)-γ-ylidenebutenolides. The reactions proceed via a formal Cu-catalyzed metalo-carboxylation process and employ simple and readily available substrates, display excellent functional group tolerance, and deliver products with high selectivity. The resulting butenolide products can be derivatized to a broad range of heterocycles.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and full characterization for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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